National Toxicology Program

U.S. Department of Health and Human Services

Annual Report 2010

National Toxicology Program

ANNUAL REPORT
For
Fiscal Year 2010

National Institute of Environmental Health Sciences
National Institutes of Health

National Center for Toxicological Research
Food and Drug Administration

National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

July 2011

Department of Health and Human Services
National Toxicology Program
NIH Publication No. 11-5972

Table of Contents

Frequently Used Abbreviations

3TC	lamivudine
AA	aristolochic acid
ACB	allele-specific competitive blocker
ACD	allergic contact dermatitis
ADME	absorption, distribution, metabolism, and excretion
Ag	silver
AMPH	amphetamine
ATSDR	Agency for Toxic Substances and Disease Registry
AZT	zidovudine, 3'-Azido-3'-Deoxythymidine
BCOP	bovine corneal opacity and permeability
BPA	bisphenol A
BrdU	bromodeoxyuridine
BSC	Board of Scientific Counselors
CASRN	CAS Registry Number
CDC	Centers for Disease Control and Prevention
CDMA	code division multiple access
CEBS	Chemical Effects in Biological Systems
CERHR	Center for the Evaluation of Risks to Human Reproduction
CNS	central nervous system
CNT	carbon nanotube
CPSC	U.S. Consumer Product Safey Commission
CYP	cytochrome P450
DA	Daicel adenosine triphosphate
DEHP	di(2-ethylhexyl) phthalate
DEP	diesel exhaust particles
DHHS	Department of Health and Human Services
DILI	drug-induced liver injury
DTBBA	dithiobisbenzanilide
ECVAM	European Centre for the Validation of Alternative Methods
EGEHE	ethylene glycol 2-ethylhexyl ether
ELISA	enzyme-linked immunosorbent assay
ENU	N-ethyl-N'-nitrosourea
EPA	Environmental Protection Agency
ESR	electron spin resonance
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FY	fiscal year
GABA	gamma-aminobutyric acid
GC/MS	gas chromatography/mass spectroscopy
GMM	Genetically Modified Model
GSM	global system for mobile communication
HHE	Health Hazard Evaluations
HPLC	high performance liquid chromatography
HTS	high throughput screening
IAG	interagency agreement
IARC	International Agency for Research on Cancer
ICATM	International Cooperation on Alternative Test Methods
ICD	irritant contact dermatitis
ICE	isolated chicken eye
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
IgE	immunoglobulin E
JaCVAM	Japanese Center for the Validation of Alternative Methods
KoCVAM	Korean Center for the Validation of Alternative Methods
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LLNA	Local Lymph Node Assay
LTKB	liver toxicity knowledgebase
mAb	monoclonal antibody
MDIG	mineral dust-induced gene
MLA	Mouse Lymphoma Assay
Mn	manganese
MOC	Memorandum of Cooperation
MOU	Memorandum of Understanding
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
MS	mass spectrometry
NASH	nonalcoholic steatohepatitis
NCGC	NIH Chemical Genomics Center
NCI	National Cancer Institute

NCTR	National Center for Toxicological Research
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NFV	nelfinavir misylate
NHGRI	National Human Genome Research Institute
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NMDA	N-methyl-D-aspartic acid
NMR	Nuclear magnetic resonance
nNOS	neuronal nitric oxide synthase
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NVP	Nevirapine
OECD	Organisation for Economic Co-operation and Development
OPA	orthophthalaldehyde
OSHA	Occupational Safety and Health Administration
PAH	polycyclic aromatic hydrocarbon
PBPK	physiologically based pharmacokinetic
PBPK/PD	PBPK/pharmacodynamic
PCBTF	chloro-4-(trifluoromethyl) benzene
PCR	polymerase chain reaction
PET	Positron Emission Tomography
PFAA	perfluoralkyl acid
PFOA	perfluorooctanoic acid
PIG-A	phosphatidylinositol glycan - complementation group A
PPAR	peroxisome proliferator-activated receptor
PWG	pathology working group
QC	quality control
qHCS	quantitative high-content screens
qHTS	quantitative high throughput screens
QSAR	quantitative SAR
RA	retinoic acid
RACB	reproductive assessment by continuous breeding
RBC/RET	red blood cell/reticulocyte
RFR	ardiofrequency radiation
RoC	Report on Carcinogens
ROS	reactive oxygen species
RP	retinyl palmitate
RPT	rabbit pyrogen test
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SAR	structure-activity relationship
SD	Sprague-Dawley
SDAR	spectrometric data-activity-relationship
SOT	Society of Toxicology
SSL	simulated solar light
STP	Society of Toxicologic Pathologists
SULT1A1	sulfotransferase 1A1
TDI	toluene diisocyanate
TiO2	titanium dioxide
TOX	NTP Toxicity Report
TR	NTP Technical Report
TRRS	Technical Reports Review Subcommittee
TZD	glitazones
UV	ultraviolet
U.S.	United States
VOC	volatile organic chemical
WC-Co	tungsten carbide-cobalt

Letter from the NIEHS/NTP Director

As I look back on NTP for FY 2010, I am pleased to let you know that our prominence within the toxicology community continues both nationally and internationally. It was a busy year, and coordination of NTP's activities with our federal partners enhanced our ability to address areas important to public health. The NTP responded immediately with coordinated efforts to address health issues associated with the Deepwater Horizon explosion and massive oil spill in the Gulf of Mexico. We initiated activities with other federal agencies to limit the adverse impacts of the oil and oil dispersants on human health, ecological health, and food sources. Early efforts by NTP focused on characterizing the toxicity of the oil and dispersants. While much progress has been made, we are continuing to tackle concerns regarding the safety of Gulf seafood, hazards to offshore and onshore cleanup workers, and potential long-term health impacts of residual oil in the environment.

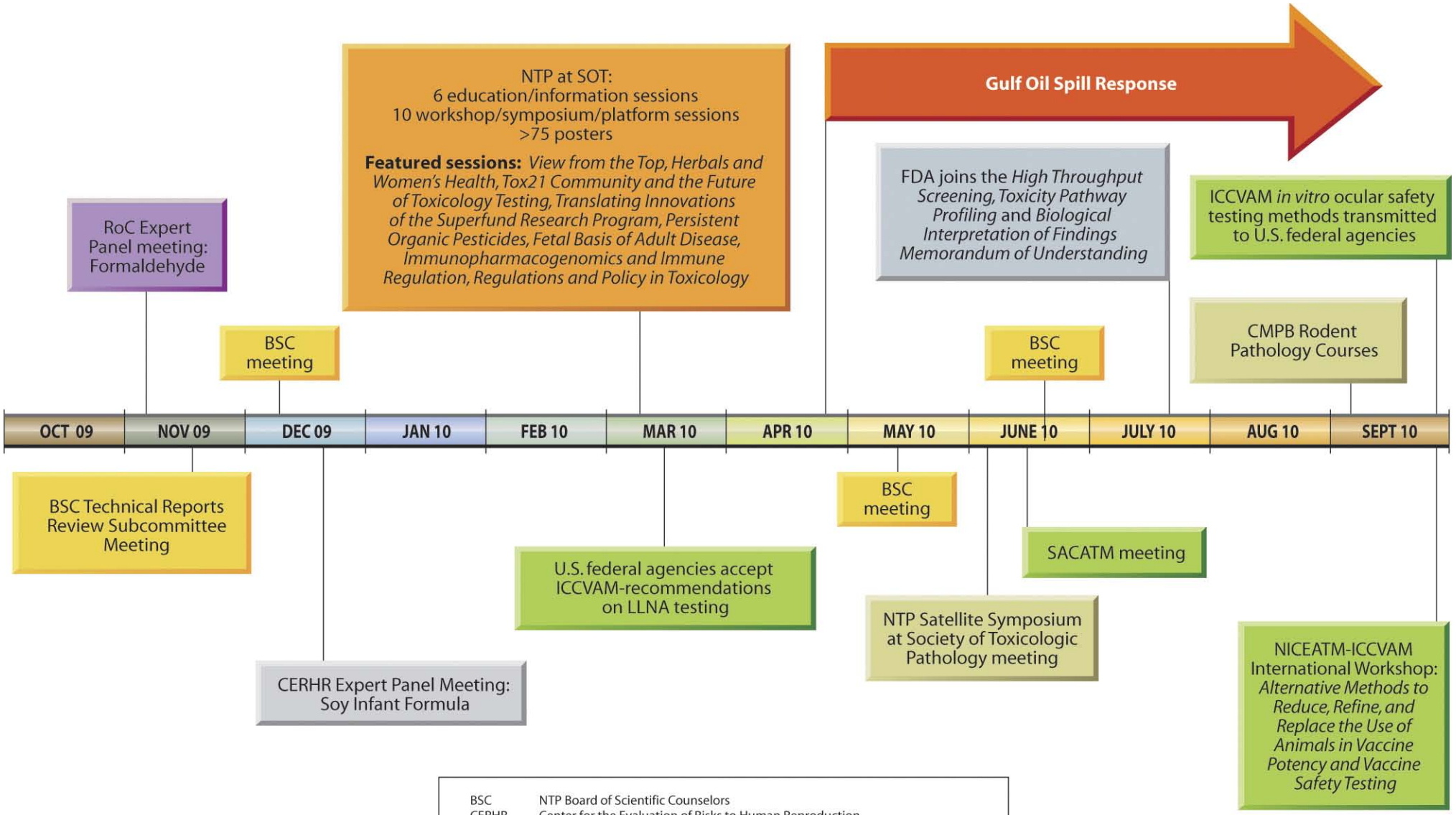
In 2010 we addressed important priorities in the President's budget, including studies of nanomaterials and alternative test evaluations through recommendations of new *in vitro* ocular safety testing methods and new contact dermatitis test methods, and a workshop on alternative methods in vaccine potency and safety testing. We also directed efforts toward NIH Director Collins' priorities in high throughput approaches, small molecule screening, and translational research. Cross-agency integration was enhanced by FDA joining the Tox21 collaboration, which merges federal research, funding, and testing tools, to develop ways to predict more effectively how chemicals affect human health and the environment. Additionally, we published ten NTP Technical Reports with the findings and conclusions from our cancer studies and introduced a more streamlined process for carrying out literature-based assessments of the potential for substances in our environment to cause adverse effects on human health.

The NTP is moving forward with new and renewed emphasis, cognizant that "Health and Environment" is a national priority. We are improving integration across research disciplines with all of our federal partners as new issues and technologies emerge. Now, and in the future, the NTP will continue to assemble the best individual and team science to address complex diseases and environmental impacts with the goal of improving our translation and communication of basic scientific findings into human health protection.

Linda Birnbaum

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.

FY 2010 Highlights, Public Meetings, and Events



BSC	NTP Board of Scientific Counselors
CERHR	Center for the Evaluation of Risks to Human Reproduction
CMPB	Cellular and Molecular Pathology Branch
FDA	U.S. Food and Drug Administration
ICCVAM	Interagency Coordinating Committee for the Validation of Alternative Methods
LLNA	Local Lymph Node Assay
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NTP	National Toxicology Program
RoC	Report on Carcinogens
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SOT	Society of Toxicology

Overview of the National Toxicology Program

Mission and Goals

Currently, the Toxic Substances Control Act Chemical Substance Inventory *(http://www.epa.gov/oppt/existingchemicals/pubs/tscainventory/index.html)*, first published in 1979, lists more than 80,000 chemicals as being available for sale and use in the United States. Approximately 850 active pesticide ingredients are formulated into approximately 17,000 pesticide products. An estimated 500 to 600 new industrial chemicals are introduced annually into U.S. commerce. The effects of many of these substances on human health are unknown, yet people and our environment may be exposed to them during their manufacture, distribution, use, and disposal or as pollutants in our air, water, or soil. While relatively few substances are thought to pose a significant risk to human health, safeguarding the public depends upon identifying the effects of these agents, and of certain naturally occurring chemicals, and determining the levels of exposure at which they may become potentially hazardous to humans.

NTP MISSION:

TO EVALUATE AGENTS OF PUBLIC HEALTH CONCERN BY DEVELOPING AND APPLYING THE TOOLS OF MODERN TOXICOLOGY AND MOLECULAR BIOLOGY

The Department of Health, Education, and Welfare (now the Department of Health and Human Services, DHHS) established the National Toxicology Program (NTP) in 1978 as a focal point to coordinate toxicology testing in the Federal government. In carrying out its mission, the NTP has several goals:

- To provide evaluations of substances of public health concern
- To develop and validate improved (sensitive, specific, rapid) testing methods
- To develop approaches and generate data to strengthen the science base for risk assessment
- To communicate with all stakeholders including government, industry, academia, the environmental community, and the public

Organizational Structure and Oversight

Three agencies, the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention, and the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (FDA), form the core for the NTP (Figure 1). The NTP is located at the NIEHS, and the Director of the NIEHS serves as the NTP Director. Questions and inquiries about the NTP can be directed to the NTP Office of Liaison, Policy and Review (919-541-7539) or *CDM@niehs.nih.gov*.

NTP Management

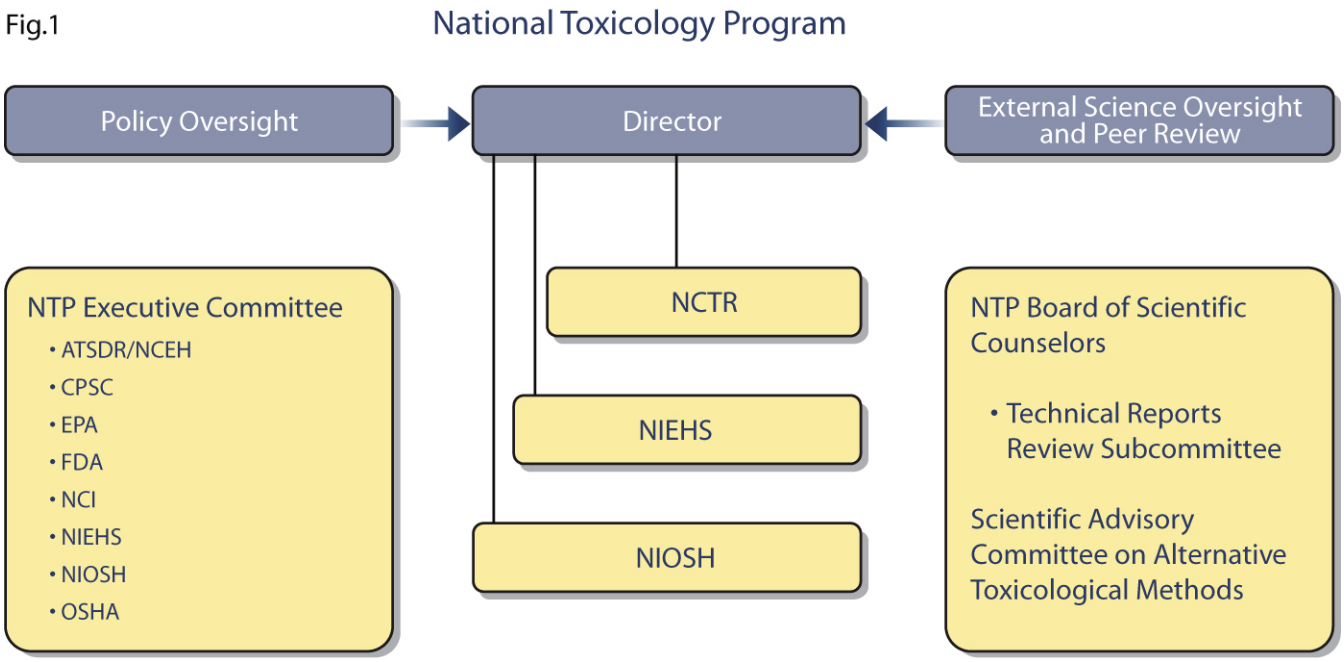
Dr. Linda Birnbaum, Director of NIEHS and NTP

Agency Program Management

NCTR: Dr. Paul Howard, Associate Director, Office of Scientific Coordination
NIEHS: Dr. John Bucher, Associate Director, NTP
NIOSH: Dr. Mark Toraason, Senior Fellow, Division of Applied Research and Technology

A list of the staff of the agencies involved with the program and their contact information are provided in Appendix 1.

Fig.1



Addressing Scientific, Regulatory, and Public Needs

The NTP is flexible and innovative in its approach toward addressing public health concerns related to exposures to chemical and physical agents at home, in the workplace, and in the environment. Over the years since its inception to take over the National Cancer Institute's (NCI's) cancer bioassy program, the NTP has expanded its scope beyond cancer to include examining the impact of substances on non-cancer outcomes, such as those affecting reproduction and development and the immune, respiratory, nervous, cardiovascular, and endocrine systems.

The NTP recognizes that initiatives addressing critical gaps in knowledge needed to evaluate environmental toxicants offer the best opportunities for preventing environmentally mediated diseases. Therefore, the NTP's testing of substances continues to evolve to include more mechanism-based toxicology studies that focus on understanding the modes of action of agents under study. In recent years, the NTP has placed a greater emphasis on providing human relevance in interpreting and understanding toxicological information created from animal or *in vitro* cell models. This is important if we are to be at the forefront in research efforts to improve methods to assess risk that account for the entire sequence of events from initial chemical exposure to ultimate toxicity.

Examples of activities the NTP covers include:

- Increased use of both information on mechanisms of action and scientific judgment in deliberations for listings in the Report on Carcinogens
- Increased efforts to examine alternative testing methods that may provide better information than current models while using fewer animals or causing less pain or distress, and may provide better data for risk assessments
- Increased efforts to collect information on (1) a broader variety of both environmental and occupational exposures, (2) potentially toxic mixtures of compounds, and (3) susceptibilities based on life stages (e.g., neonatal, elderly)

Internationally, the NTP rodent bioassay is recognized as the standard for identifying carcinogenic agents; however, the NTP continues to work to reduce, refine, and replace the use of experimental animals and to develop and validate alternative testing methods. This effort led to the creation of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) in 1998. The NTP will continue to work with the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) through NICEATM in promoting the development, validation, and regulatory acceptance of new and revised alternative toxicological methods.

Strengthening existing partnerships and forging new ones are important to achieve NTP goals. Partnerships with other sister Federal agencies are increasing (interagency agreements [IAGs] are presented on page 78). The NTP continues to support an effort to evaluate the phototoxicity of various compounds through the NTP Center for Phototoxicology at the NCTR. The NTP is also contributing to toxicological assessments of emerging issues such as nanotechnology, radiofrequency radiation emissions from cellular phones, herbal medicines/dietary supplements, water disinfection by-products, and phthalates, and will provide this information to other agencies.

Regulatory agencies make decisions to protect public health based on scientific information from several sources (e.g., toxicology, human studies, and basic research). The NTP plays a critical role in providing needed scientific data, interpretation, and guidance in the appropriate uses of these data, to regulatory agencies as well as other groups involved in health-related research. The NTP is committed to using the best science available in setting priorities for future studies and in designing, conducting, and interpreting the findings of those studies. The American people and government agencies at state and Federal levels rely on the NTP to provide a strong scientific basis for making credible decisions that will protect public health. The NTP maintains an objective, science-based approach in dealing with critical issues in toxicology and is recognized by many groups for its scientific rigor, objectivity, and open approach in the continuing dialogue on appropriately applying scientific advances to applied toxicology research and testing.

Communication and Public Outreach

Maintaining open communications and ensuring dialogue with Federal and state agencies, industry, nongovernment groups, academia, and the public are goals of the NTP. NTP advisory groups (see page 8) provide regular scientific and public peer review and input. NTP conferences and workshops remain a priority and are designed to bring researchers, regulators, policy makers, and the public together to examine issues and achieve consensus on future directions in toxicology and risk assessment.

Distribution of NTP study results, program plans, initiatives, announcements, press advisories, and publications is accomplished in several ways to communicate as much as possible with the public. Information is routinely distributed to interested parties through *Federal Register* announcements on the NTP website (*http://ntp.niehs.nih.gov*). The website offers access to information about the program that details and highlights ongoing and

future initiatives, announcements, NTP centers, NTP publications, and study data. The public can subscribe to the NTP ListServ on the website to receive news and updates. Currently the ListServ has more than 4,000 subscribers. The NTP publishes the quarterly newsletter, *NTP Update*, which can be downloaded from the NTP website. NTP actively participates in the annual Society of Toxicology (SOT) meeting. At the 2010 SOT meeting in Salt Lake City, Utah, NTP staff participated in ten workshop/symposium/platform sessions, six education/information sessions, and presented more than 75 posters.

The NIEHS/NTP Central Data Management Office oversees distribution (upon request) of specific chemical study information and printed NTP documents – NTP study status reports, final and draft copies of NTP Technical Report Series, and background documents for substances nominated to the NTP for study. On-line, searchable access is available for the Report on Carcinogens (RoC) and the NTP Technical, Toxicity, and Genetically Modified Models series reports (*http://ntp.niehs.nih.gov)*. In FY 2010, 823,914 reports and other PDF documents were downloaded from the NTP website. Approximately one third of the requests were for documents related to the RoC.

The NTP is interested in and welcomes stakeholder input into its programs and priorities. Nominations, inquiries, and comments from the public and other interested parties are encouraged at any time. The NTP Office of Liaison, Policy and Review at the NIEHS under the direction of Dr. Mary S. Wolfe serves as the focal point for receiving input to the program and for overseeing the distribution of information about programs, workshops, initiatives, and other NTP projects.

NTP Office of Liaison, Policy, and Review
NIEHS/NIH
MD K2-03
111 TW Alexander Drive, RTP, NC 27709
Phone: (919) 541-7539
wolfe@niehs.nih.gov

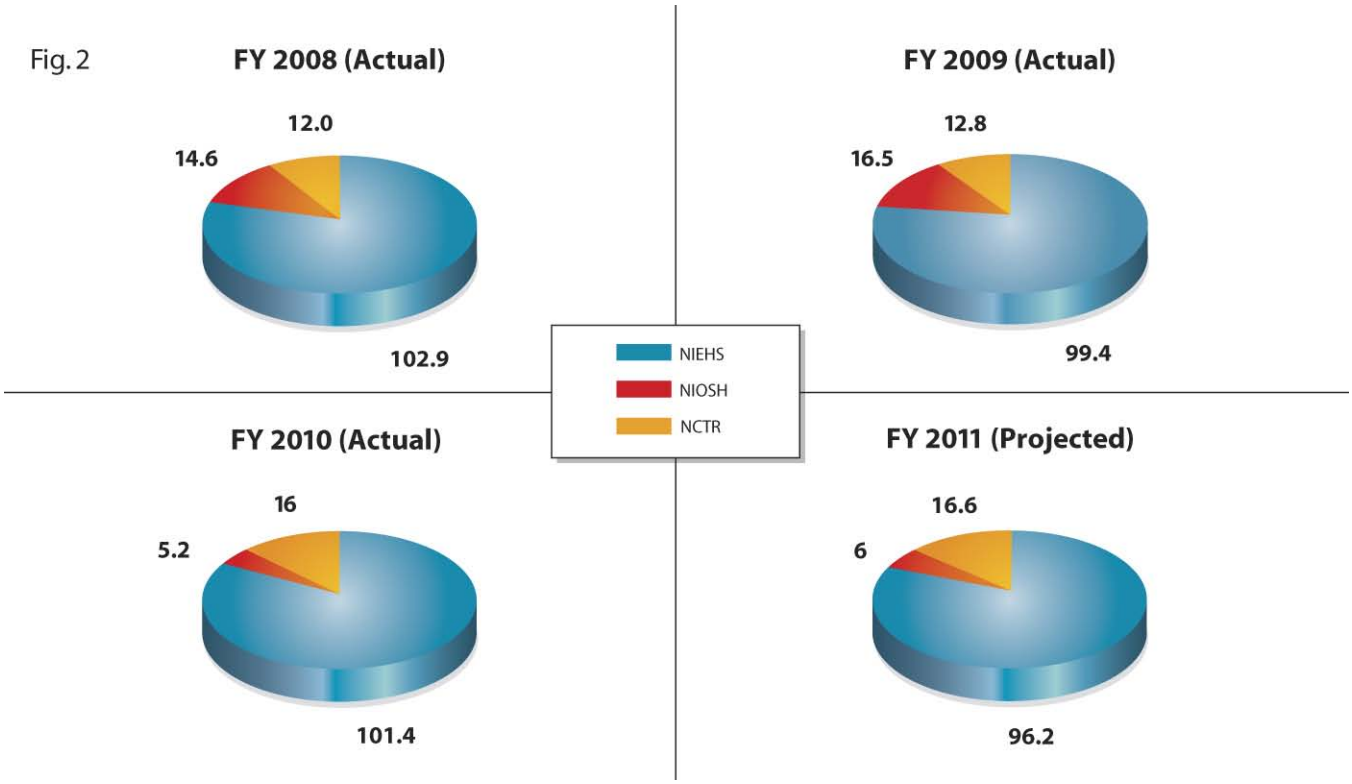
Central Data Management
NIEHS/NIH
MD K2-05
111 TW Alexander Drive, RTP, NC 27709
Phone: (919) 541-3419
cdm@niehs.nih.gov

Resources and Planning

Current and Projected Research Capacity

The NTP relies on voluntary allocations from the program's three core agencies (NIEHS, NCTR, and NIOSH) to support its various programs and initiatives. These allocations are specified after yearly appropriations are determined. As shown in Figure 2, the actual total allocations from the principals toward the NTP dropped from FY 2009 to FY 2010. For FY 2011, a 2% decrease in funding from FY 2010 levels is projected. FY 2011 funding is estimated to be 92% of FY 2008 funding. The NTP conducts its research studies mainly through contract laboratories or in-house at the core agencies, but also supports IAGs with other Federal agencies. Funds are used to sponsor workshops and conferences and to produce and distribute printed programmatic materials. In FY 2010, the NIEHS funded 46 contracts and held one workshop and two expert-panel meetings for the NTP. The NIEHS also funded IAGs with NIOSH, NCTR, EPA, and the NIH Chemical Genomics Center (NCGC) and held five scientific advisory meetings.

Fig. 2



The NTP maintains an objective, science-based approach in dealing with critical issues in toxicology and continually sets priorities to improve the nation's ability to evaluate the human health effects caused by environmental exposures.

In summary, the NTP is a comprehensive research program spanning several agencies committed to providing resources to support the NTP's research and to communicating the knowledge learned to all stakeholders, public and private. The NTP's efforts in testing, research, and assessing health hazards work to obtain the best scientifically valid data for health regulatory and research agencies to use to make appropriate decisions about potential human risks from exposure to environmental toxicants. Toward that end, the NTP is continually evolving to remain at the cutting edge of scientific research and development and application of technology.

Advisory Boards and Committees

As shown in Figure 1 (page 4), the NTP relys on a number of external boards and committees for science and policy oversight and peer review. As needed, the program convenes Special Emphasis Panels and Working Groups to address specific topics.

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC), a Federally chartered advisory group, provides scientific oversight to the NTP, including the RoC Center and the Center for the Evaluation of Risks to Human Reproduction (CERHR). The Secretary of DHHS appoints members to the BSC. The BSC can consist of up to 35 scientists, primarily from the public and private sectors, with scientific expertise relevant to the NTP's activities. The BSC members serve rotating terms of up to four years and the BSC typically meets two to three times per year. Opportunities for public comment are scheduled at all meetings. The BSC's Technical Reports Review Subcommittee (TRRS), which provides peer review of draft NTP long-term toxicology and carcinogenesis technical reports, met once during FY 2010. Following that meeting, the subcommittee was discontinued and beginning in FY2011, the peer review of the draft NTP Technical Reports will be done through expert peer review panel meetings. Dr. Lori White, the NTP Designated Federal Officer, manages the BSC. A list of members during FY 2010 is provided in Table 1.

BSC members and NTP staff at the June 2010 BSC meeting.

BSC meetings in FY 2010

The BSC met three times in FY 2010 at NIEHS in Research Triangle Park, NC. Complete information about the meetings can be obtained at *http://ntp.niehs.nih.gov/go/9741*.

On December 9 – 10, 2009, the BSC reviewed the NTP Host Susceptibility Branch research and testing program, two contract concepts (analytical chemistry support and laboratory studies to evaluate toxicity following early life exposure to chemicals), CERHR's revised evaluation process and proposed concept for a workshop on the effect of environmental exposures on diabetes and obesity, concepts for five testing program nominations (butterbur, evening primrose oil, hydroquinone, silica flour, and valerian extracts and oil), and NTP's Dietary Supplement and Herbal Medicine Initiative.

The BSC met on May 10, 2010, to peer review the draft NTP Brief on Soy Infant Formula. The BSC also reviewed two CERHR proposals at that meeting, a research concept for assessing isoflavones in soy infant formula, and an approach for evaluating health effects of low-level lead exposure. The BSC also approved the TRRS report from the November 19, 2009 meeting.

At the June 21 – 22, 2010 meeting, the BSC peer reviewed draft substance profiles for three substances proposed for inclusion in the 12th Report on Carcinogens, glass wool fibers, formaldehyde, and cobalt-tungsten carbide: powders and hard metals. The BSC also reviewed a CERHR proposal for an evaluation of cancer chemotherapy during pregnancy, the NTP Chemical Effects in Biological Systems (CEBS) Data Management System, and a research concept for hydroxyurea.

TRRS meeting in FY 2010

The BSC TRRS met in public forum on November 19, 2009, at the NIEHS. The subcommittee peer reviewed the findings and conclusions of six draft NTP Technical Reports (1-bromopropane, ginseng, pulegone, milk thistle extract, bis(2-chloroethoxy)methane, diethylamine) of studies that used conventional rodent models. The subcommittee's recommendations were reported to the BSC at the May 10, 2010 meeting.

Table 1. NTP Board of Scientific Counselors Membership Roster FY 2010

Name and Title	Affiliation	Term Ends	BSC Service
Tracie E. Bunton, DVM, PhD, DACVP Toxicology Consultant	Eicarte LLC Fairfield, PA	12/27/10	BSC and TRRS
Edward W. Carney, PhD Technical Leader, Developmental, Reproductive and General Toxicology	The Dow Chemical Company Midland, MI	12/27/10	BSC
Russell C. Cattley, VMD, PhD Executive Director Pathology	Amgen Thousand Oaks, CA	12/27/10	BSC and TRRS
David A. Eastmond, PhD Professor and Chair, Department of Cell Biology and Neuroscience	University of California Riverside, CA	06/30/12	BSC and TRRS
Janan T. Eppig, PhD Senior Staff Scientist	The Jackson Laboratory Bar Harbor, ME	06/30/12	BSC
Elaine M. Faustman, PhD Professor and Director, Institute for Risk Analysis and Risk Communication; Department of Environmental and Occupational Health Sciences	University of Washington Seattle, WA	06/30/12	BSC
George Friedman-Jiménez, MD Assistant Professor, Departments of Environmental Medicine and Medicine	New York University School of Medicine New York, NY	12/27/09	BSC
William P. Janzen Professor, Division of Medicinal Chemistry and Natural Products; Director, Assay Development and Compound Profiling	University of North Carolina at Chapel Hill, NC	06/30/10	BSC
Stephen W. Looney, PhD Professor, Department of Biostatistics, Department of Oral Health and Diagnostic Science	Medical College of Georgia Augusta, GA	06/30/12	BSC and TRRS
Mitzi Nagarkatti, PhD Professor and Chair, Department of Pathology, Microbiology and Immunology	University of South Carolina School of Medicine Columbia, SC	12/27/11	BSC and TRRS
Raymond F. Novak, PhD (chair 1/10 – 12/10) Director, Institute of Environmental Health Sciences	Wayne State University Detroit, MI	12/27/10	BSC and TRRS

Name and Title	Affiliation	Term Ends	BSC Service
Michael V. Pino, DVM, PhD Director of Pathology	Sanofi-Aventis Bridgewater, NJ	12/27/09	BSC and TRRS
Kenneth M. Portier, PhD (chair 1/09 – 12/09) Director of Statistics	American Cancer Society Atlanta, GA	12/27/09	BSC and TRRS
Jim E. Riviere, DVM, PhD, ATS Burroughs Wellcome Fund Distinguished Professor of Pharmacology	North Carolina State University Raleigh, NC	12/27/09	BSC and TRRS
Diane M. Robins, PhD Professor, Department of Human Genetics	University of Michigan Medical School Ann Arbor, MI	12/27/09	BSC
Ruthann A. Rudel, MS Senior Scientist, Toxicology and Environmental Health Risk Assessment	Silent Spring Institute Newton, MA	12/27/11	BSC
James L. Sherley, MD, PhD Senior Scientist	Boston Biomedical Research Institute Watertown, MA	06/30/11	BSC and TRRS
Gina M. Solomon, MD, MPH Senior Scientist	Natural Resources Defense Council San Francisco, CA	12/27/11	BSC
Justin G. Teeguarden, PhD Senior Scientist, Fundamental and Computational Sciences Directorate	Pacific Northwest National Laboratory Richland, WA	12/27/11	BSC and TRR

NTP Board of Scientific Counselors Pending Members, FY 2010

Name and Title	Affiliation	Term Ends	BSC Service
Miguel C. Fernández, MD, FACEP, FAAEM, FACMT, FAACT Professor of Surgery, Division of Emergency Medicine	University of Texas Health Science Center San Antonio TX	06/30/13	BSC
Nicholas P. Jewell, PhD Professor of Biostatistics and Statistics	University of California Berkeley, CA	06/30/13	BSC
Dana Loomis, PhD Professor and Chair, Department of Epidemiology	University of Nebraska Medical Center Omaha, NE	06/30/12	BSC
Melissa A. McDiarmid, MD, MPH Prof. of Epidemiology and Preventive Medicine Director, Occupational Health Program	University of Maryland School of Medicine Baltimore, MD	06/30/13	BSC
Lisa Minor, PhD	*In Vitro* Strategies, LLC Flemington, NJ	06/30/13	BSC
Richard Miller, DVM, PhD Vice President, Safety Assessment	GlaxoSmithKline Research Triangle Park, NC	06/30/13	BSC
Judith Zelikoff, PhD Professor, Environmental Medicine Director, Community Outreach	New York University School of Medicine Tuxedo, NY	06/30/12	BSC

Additional information about the BSC, including minutes from its meetings, is available on the NTP website *http://ntp.niehs.nih.gov/go/164* or from Dr. Lori White, BSC Designated Federal Officer (*whiteld@niehs.nih.gov*).

Scientific Advisory Committee on Alternative Toxicological Methods

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory committee established on January 9, 2002, in response to the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3(d)). SACATM advises ICCVAM, NICEATM, and the Director of the NIEHS regarding statutorily mandated duties of ICCVAM and activities of NICEATM (see page 44). SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. Alternative methods are those that reduce, refine (lessen or avoid pain and/or distress), or replace the use of animals in testing. SACATM also provides input on ways to foster partnerships and communication with interested parties. The NIEHS Director appoints 15 voting members to the SACATM, and membership includes representatives drawn from academia, state government, industry, and animal protection organizations. A list of members during FY 2010 is provided in Table 2. SACATM typically meets once a year and members serve rotating terms of up to four years. Dr. Lori White, NTP Designated Federal Officer, manages SACATM.

Members of SACATM and ICCVAM, international liaisons, and NIEHS/NTP staff at the June 2010 SACATM meeting.

SACATM met on June 17 – 18, 2010, at the U.S. Environmental Protection Agency (EPA) in Research Triangle Park, NC. SACATM members discussed a number of important issues including the validation of alternative methods for assessing chemically induced eye injuries, assessment of acute and chronic pain in laboratory animals, and alternative methods of vaccine potency testing. Representatives from the FDA National Center for Toxicological Research and NIEHS/NTP presented updates on their current research activities including high throughput screening, validation of endocrine disruptor test methods, new model systems, approaches to identify biomarkers of disease and toxicity, and bio-imaging. Liaisons from Health Canada, the European Centre for the Validation of Alternative Methods (ECVAM), and the Korean Center for the Validation of Alternative Methods (KoCVAM) presented updates on the activities of their groups.

Table 2. Scientific Advisory Committee on Alternative Toxicological Methods Roster, FY 2010		
Name and Title	**Affiliation**	**Term Ends**
Laura Andrews, PhD, DABT Vice President, Pharmacology and Toxicology	Genzyme Corporation Framingham, MA	06/30/12
Karen K. Brown, PhD President	Pair O' Docs Enterprises Parkville, MO	06/30/11
George B. Corcoran, PhD, ATS Professor and Chairman Department of Pharmaceutical Sciences	Wayne State University Detroit, MI	06/30/11
Helen E. Diggs, DVM, DACLAM Associate Dean, Hospital Program Director Veterinary Teaching Hospital	College of Veterinary Medicine, Oregon State University Corvallis, OR	06/30/10
Marion F. Ehrich, PhD Professor, Biomedical Sciences and Pathology/Laboratory for Neurotoxicity Studies	VA-MD Regional College of Veterinary Medicine Blacksburg, VA	06/30/10
Eugene L. Elmore, PhD Senior Project Scientist Department of Radiation Oncology	University of California Irvine, CA	06/30/12
James Freeman, PhD (chair) Distinguished Toxicology Associate	ExxonMobil Biomedical Sciences, Inc. Annandale, NJ	06/30/10
Steven R. Hansen, DVM, MS, MBA, DABT, ABVT Chief Operating Officer	American Society for the Prevention of Cruelty to Animals Urbana, IL	06/30/12
Gwendolyn Y. McCormick, DVM, MS, DACLAM Attending Veterinarian and Distinguished Research Fellow Animal Resources Department	Boehringer Ingelheim Pharmaceuticals, Inc Ridgefield, CT	06/30/12
Sharon A. Meyer, PhD Associate Professor, Department of Toxicology	The University of Louisiana at Monroe Monroe, LA	06/30/11
Steven M. Niemi, DVM Director, Center for Comparative Medicine	Massachusetts General Hospital Charlestown, MA	06/30/11
Michael J. Olson, PhD, ATS Director, Occupational Toxicology Corporate Environment, Health, Safety and Sustainability	GlaxoSmithKline Research Triangle Park, NC	06/30/13
Annie (Peiyong) Qu, PhD Associate Professor, Department of Statistics	University of Illinois at Urbana-Champaign Champaign, IL	06/30/10
Linda A. Toth, DVM, PhD Associate Dean for Research and Faculty Affairs Professor Department of Pharmacology	Southern Illinois University School of Medicine Springfield, IL	06/30/13
Gary Wnorowski, MBA, LAT President	Eurofins/Product Safety Laboratories Dayton, NJ	6/30/11

Additional information about SACATM, including minutes from its meetings, is available on the NTP website *http://ntp.niehs.nih.gov/go/167* (select "Advisory Board and Committees") or from Dr. Lori White, Designated Federal Officer, NIEHS *(whiteld@niehs.nih.gov)*.

NTP Executive Committee

The NTP Executive Committee provides programmatic and policy oversight to the NTP Director. The Executive Committee meets once or twice a year in closed forum. Members of this committee include the heads (or their designees) of the following Federal agencies:

- U.S. Agency for Toxic Substances and Disease Registry/National Center for Environmental Health
- U.S. Consumer Product Safety Commission
- U.S. Environmental Protection Agency
- U.S. Food and Drug Administration
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Institute for Occupational Safety and Health
- Occupational Safety and Health Administration

To enhance agency interactions, in FY 2010 the NTP began using agency Points of Contact (POCs) in lieu of formal committees to streamline communication and better utilize agency staff. Agency POCs have a dedicated responsibility and time commitment, are knowledgeable about the NTP mission and programs and their agency's resources, and allow the most relevant agency expertise to be brought to bear on NTP issues. The responsibilities of the Interagency Committee for Chemical Evaluation and Coordination were assumed by the agency POCs.

Interagency Coordinating Committee on the Validation of Alternative Methods

ICCVAM is a permanent interagency committee of the NIEHS under NICEATM. The committee was formally established by the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3). The purpose of ICCVAM is to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness (see http://iccvam.niehs.nih.gov/about/process.htm). ICCVAM meets several times per year and consists of representatives from 15 Federal agencies that generate or use toxicological data to carry out their responsibilities to protect and improve the health and safety of people, animals, and the environment:

- U.S. Agency for Toxic Substances and Disease Registry/National Center for Environmental Health
- U.S. Consumer Product Safety Commission
- U.S. Department of Defense
- U.S. Department of Agriculture
- U.S. Department of Energy
- U.S. Department of the Interior
- U.S. Department of Transportation
- U.S. Environmental Protection Agency
- U.S. Food and Drug Administration
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Institutes of Health
- National Institute for Occupational Safety and Health
- National Library of Medicine
- Occupational Safety and Health Administration

NIOSH/NTP

NIOSH/NTP: Division of Applied Research and Technology

NIOSH/NTP: Division of Surveillance, Hazard Evaluations, and Field Studies

NIOSH/NTP: Health Effects Laboratory Division

The National Institute for Occupational Safety and Health (NIOSH) is the Federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. The mission of NIOSH is to generate new knowledge in the field of occupational safety and health and to transfer that knowledge into practice for the betterment of workers. To accomplish this mission, NIOSH conducts scientific research, develops guidance and authoritative recommendations, distributes information, and responds to requests for workplace Health Hazard Evaluations (HHEs).

NIOSH's participation in the NTP is consistent with its mandate to protect workers' health and safety under the Occupational Safety and Health Act and the Federal Mine Safety and Health Act. Setting priorities in occupational toxicological research is based upon several sources of information that are developed and maintained by NIOSH, including HHEs, industry-wide studies, gaps in knowledge identified while developing criteria for recommended standards or Criteria Documents, Current Intelligence Bulletins, hazard reviews or alerts, other technical reports, and information profiles on chemical hazards. Toxicological research on important occupational chemicals is conducted in genetic toxicology, carcinogenesis, toxicological characterization, chemical disposition, biological monitoring, reproductive and developmental toxicology, dermal toxicology, and exposure assessment. NIOSH research projects are conducted by the:

- Division of Applied Research and Technology – Cincinnati, Ohio
- Division of Surveillance, Hazard Evaluations, and Field Studies – Cincinnati, Ohio
- Education and Information Division – Cincinnati, Ohio
- Health Effects Laboratory Division – Morgantown, West Virginia

NIOSH/NTP studies funded by NIOSH voluntary contributions are listed in Table 3.

Table 3: NIOSH/NTP Projects FY 2010

NIOSH/NTP Project [Project Officer]	Objective and/or Project Summary
Reproductive Health Assessment of Male Workers [Schrader]	To evaluate reproductive health hazards using a health profile consisting of biomarkers for assessing male fecundity. Current efforts will focus on completing the Longitudinal Investigation of Fertility and the Environment (LIFE) project, which is a collaborative effort between NIOSH and the NICHD/NIH. This work includes development of new biomarkers to include in the male reproductive health profile.
Immunochemical Biological Monitoring for Occupational Exposure and Disease [Striley]	To evaluate industrial and agricultural chemicals with known acute and chronic toxicities which present a significant exposure risk for workers. Biological monitoring can assess exposure by analyzing acute and latent metabolites in various biological media. The goal of this project is to develop low-cost, rapid immunochemical and analytical chemistry biomonitoring methods that will be used to identify exposures and evaluate potential interventions. Concurrent with development of exposure assessment methods, this project will identify and develop new multiplex immunochemical methods to evaluate biomarkers of occupational illness or subclinical signs of occupational illness.
Orthophthalaldehyde (OPA) Hazard Assessment [Toraason]	To conduct an assessment of occupational exposures to OPA and to determine if healthcare workers are experiencing adverse effects associated with exposure. To assess exposure, this study will also develop analytical methods for environmental monitoring of OPA and determine the feasibility of an OPA biomarker. Because of the absence of published toxicological data on OPA, testing will be conducted in experimental animals. The toxicological testing will focus on dermal and respiratory irritation and sensitization. Dose-response data will be obtained for hazard identification risk assessment, which, along with health assessments, will serve as the basis for establishing exposure limits.
UV Native Fluorescence-Based Monitor for Workplace Exposures [Snawder]	To develop and evaluate a readily adaptable, next generation, direct reading, personal monitor for use in measuring worker exposure to a wide variety of chemicals including naphthalene and components of asphalt fume. The development of a monitor for volatile and semi-volatile workplace chemicals will be helpful in rapidly assessing chemical exposure and will result in more realistic occupational exposure assessments and allow for rapid interventions leading to reduced worker exposures and thus preventing occupational illness and disease.
Analytical Research & Development Infrastructure [Streicher]	To provide for the administrative needs and analytical instrumentation repair and maintenance in support of Chemical Exposure and Monitoring Branch chemists conducting research on sampling and analytical methods development for workplace chemicals. New methods needed to assess chemicals being investigated as part of the NIOSH/NTP exposure assessment IAG are developed in this project.
Diacetyl Exposure Assessment [Streicher]	To develop and evaluate sampling and analytical methods for diacetyl and other flavoring compounds to enable accurate exposure assessment and evaluation of the effectiveness of control technology. Two sampling and analytical methods are being investigated for measurement of specific flavoring compounds, most notably diacetyl and 2,3-pentanedione in airborne particles and bulk powders. Finally, broader GC/MS method(s) will be developed for a range of compounds present in flavorings.
Chemical Exposure Monitoring with Indoor Positioning [Brown]	To investigate a direct reading exposure method that uses a personal photo ionization detector chemical monitor with telemetry and an indoor positioning system to provide remote monitoring of a worker's exposure to volatile organic chemicals (VOCs) with position and time. The personal monitor continuously samples and analyzes the workers breathing zone air for VOCs while recording their position and time of exposure. Indoor positioning is accomplished using a radio transmitter attached to the personal monitor and receivers place in the ceiling corners of the room. The positioning receivers communicate with each other and a remote laptop using wireless local area network (WLAN) technology. The remote laptop calculates and visualizes the worker position and exposure level. Once developed, this technology will be applied to analyze workplace exposures to diacetyl.

NIOSH/NTP Project [Project Officer]	Objective and/or Project Summary
Titanium Dioxide (TiO_2) Nanoparticle Exposure Study [Curwin]	To collect occupational exposure information for workers exposed to ultrafine and fine TiO_2. The data will be used by the Education and Information Division to provide information for the Current Intelligence Bulletin on TiO_2. The study objectives are (1) to develop a strategy to measure exposure to ultrafine particles, (2) to characterize exposure to ultrafine and fine TiO_2 for various jobs and tasks at various facilities manufacturing and using TiO_2, and (3) to evaluate a strategy for measuring workplace exposure to fine and ultrafine TiO_2.
Exposure Assessment for Toxicologically Important Chemicals [Estill]	To characterize workplace exposures to welding fumes with emphasis on manganese, indium and indium compounds, diacetyl; 2-methoxy-4-nitroaniline, and 2′, 2‴-dithiobisbenzanilide, all of which have been nominated by various groups to the NTP. NIOSH will identify possible candidate industries, labor unions, workplaces, and uses and users; will determine if there is relevance for occupational health; estimate the number of workers exposed; and perform limited workplace exposure sampling.
Exposures and Engineering Controls in the Flavoring Industry [Curwin]	To conduct a complete exposure assessment, evaluate potential engineering controls within the flavoring industry, and create appropriate work practice advice to reduce occupational exposures in these industries. Although a dose response curve for various flavoring compounds and associated health effects has not been established, improved work practices and engineering control advice can minimize occupational exposures. Data from initial research efforts have been very useful in preliminary rulemaking efforts for both OSHA and Cal-OSHA.
Development of New Immunodiagnostic and Detection Techniques for Indoor Fungi [Green]	To address problems associated with measuring personal exposure to *Paecilomyces variotii* fungus in occupational settings by identifying the major allergens and to produce species-specific monoclonal antibodies towards these allergens. These antibodies will then be used to create practical immunoassays to detect this fungus in clinical and environmental samples.
Cutaneous Bioactivation of Xenobiotics: Hapten vs. Prohapten [Siegel]	To develop an *in vivo* model of allergic skin sensitization that can discriminate between chemicals requiring metabolic activation for sensitization (prohaptens) and those that can sensitize without biological activation (haptens). The model will involve the dermal application of various pharmacological inhibitors of the cytochrome P450 (CYP) pathway prior to performing either the local lymph node assay (LLNA) or/and mouse ear swelling test. Selective inhibition of the CYP pathway should distinguish between direct acting haptens and metabolically activated pro-haptens. Validation of the models will be done using known direct acting haptens and prohaptens. Successful development of these models will produce data that strengthens *in silico* hazard predictive models and allows for substitution or modification of allergenic chemicals and drugs.
Immunotoxicological Evaluation of Occupational Chemicals [Anderson]	To identify occupational and environmental chemical hazards and evaluate immune function and mechanism associated with exposure. This research will contribute to increased identification of immunological hazards encountered in the workplace. Further evaluation of these compounds will allow for better risk assessment, which will ultimately establish occupational exposure limits.
Evaluation of Perfluoralkyl Acids (PFAAs) Immunotoxicity [Franko]	To investigate perfluorooctanoic acid (PFOA), which is no longer used in manufacturing, but still persistent in the environment, and which has been shown in a murine model to be both immunosuppressive and to have a potential role in asthma and allergy. Due to the potential health effects linked to PFOA exposure, replacement PFAAs are now being used in the manufacturing process but little is known about what effects these compounds will have on immune function. This project will evaluate the immunotoxic effects associated with individual PFAAs that are still in use, and will investigate the mechanism mediating the identified immunological alterations associated with PFOA exposure.

NIOSH/NTP Project [Project Officer]	Objective and/or Project Summary
Airway Fungal Exposure and Allergic Sensitization in Mice [Templeton]	To compare the immunological health effects of lung exposure to fungal spores or hyphal fragment preparations. Agricultural, as well as construction and remediation workers, are exposed to elevated levels of fungi and can experience rhinitis, respiratory allergic symptoms, and/or asthma as a result of their exposure. This project will have two major areas of study: (1) determination of the health effects following aspiration of hyphal fragments from *Stachybotrys chartarum* and *Alternaria alternata* in the absence of intact spores in mice, and (2) comparison of the ability of aspirated spores or hyphal suspensions from *Aspergillus* spp., *S. chartarum*, and *A. alternata* to exacerbate respiratory allergy to ovalbumin.
Transient Dermal Exposure: Model and Experiments [Frasch]	To enhance knowledge and understanding of how industrial chemicals penetrate the skin after the types of exposure that occur in occupational settings. Data from *in vitro* skin penetration experiments will be compared with predictions of computer models to enhance their predictive value. A final product of this research will be a user-friendly, interactive, web-based calculator that can estimate the amount of chemical that penetrates the skin during workplace exposures.
Indoor Chemistry of Consumer Product Mixtures [Wells]	To investigate indoor reactant/consumer product reactions to more clearly define indoor workplace exposure, provide insight into important chemical structure(s) that influence indoor air quality, and highlight potential analytical/sampling needs. The research direction will be influenced by indoor environment research, such as indoor pollutant characterization and measurements. The research results will yield more accurate exposure assessments, better analytical tools for HHE sampling, and improved engineering control methods to reduce chemical contaminants.
Immune and Inflammatory Aspects of Occupational Rhinitis [Johnson]	To understand the mechanisms of occupational rhinitis in occupational safety, health, and medicine. A combined study design using human and animal research will be employed to identify the orthologously conserved pathways and gene networks that characterize the pathobiology of occupational rhinitis induced by diisocyanates. The outcomes of this research will benefit occupational safety and health through improved diagnosis and prevention of allergic airways disease caused by diisocyanates.
Genetics in Occupational Diseases [Yucesoy]	To investigate susceptibility gene variants that contribute to the development and severity of occupational irritant contact dermatitis (ICD) and asthma using high density and high throughput genotyping platforms. Previous and on going studies showed that cytokine polymorphisms have a major influence on silicosis, dementia, accelerated decline in lung function, and vaccine efficacy. Understanding the genetic contribution to the development, progression, and outcomes of complex occupational diseases will help improve the accuracy of risk assessment and improve safe exposure levels for genetically susceptible groups in the workforce.
Investigation of the Genetic Fingerprint of Chemically-induced and Spontaneously-occurring Lung Cancer Using a Mouse Model [Reynolds]	To determine if there are different carcinogen-specific chromosomal (genetic) markers in spontaneously-occurring and chemically-induced mouse lung adenocarcinomas. Mice were exposed by inhalation to vanadium pentoxide, nickel oxide, or cumene (a benzene derivative), three chemicals to which workers in the construction and manufacturing sectors are exposed. NIOSH will analyze mouse lung tumors induced by single-wall carbon nanotubes (SWCNTs). Results from these studies will be used to establish biomarkers for early detection and therapeutic intervention of lung cancer in workers.
Workplace Exposure, Inflammation, and Cardiovascular Toxicity [Simeonova/Erdely]	To investigate particle-respiratory tract exposure that has been related to increased mortality from cardiovascular diseases. This laboratory-based research will evaluate novel molecular mechanisms involved in the link between occupational exposures to ultrafine/nanosize particulates and the development of cardiovascular diseases. Planned studies will help to identify potential risk factors, biomarkers, and specific targets for prevention and therapeutic intervention of occupationally related cardiovascular diseases.

NCTR/NTP

NCTR/NTP

The National Center for Toxicological Research (NCTR), the FDA's research center, plays a critical role carrying out the agency's mission. NCTR, in partnership with researchers from elsewhere in FDA, other government agencies, academia, and industry, provides innovative technology, methods development, vital scientific training, and technical expertise. The unique scientific expertise of NCTR is critical in supporting FDA product centers and their regulatory roles. NCTR conducts an array of studies that reflect the NTP mission statement.
These NCTR/NTP studies, funded by NCTR voluntary allocations, are listed in Table 4.

Table 4: NCTR/NTP Projects in FY 2010*

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
DNA Adduct Formation, Mutations, and Patterns of Gene Expression in Big Blue Rats Treated with the Botanical Carcinogens Riddelliine, Aristolochic Acid (AA), and Comfrey [Chen]	(1) To treat Big Blue rats subchronically with riddelliine, AA, and comfrey using procedures appropriate for tumor induction, (2) to analyze DNA adduct formation in the target tissues for carcinogenesis and in spleen lymphocytes, (3) to determine the cII™ mutant frequencies and the types of cII™ mutations in the target tissues of treated rats, (4) to determine global gene expression patterns in the target and surrogate tissues of treated rats, and (5) to correlate gene expression patterns with DNA adduct formation and mutation induction in treated rats.
Further Evaluation of the Types of Genetic Events Detected by the Mouse Lymphoma Assay (MLA) and the Role of the Assay in Mechanistically-based Risk Assessment [Moore]	(1) To determine if the L5178Y/TK+/- MLA adequately detects both aneuploidy and mitotic recombination, (2) to determine if L5178Y mouse lymphoma cells have active recombinase functions which lead to a large proportion of mutants that result from recombinase-mediated rearrangements, and (3) to determine the fundamental genetic mechanism(s) causing the small and large colony thymidine kinase mutant phenotypes.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Evaluation of Novel Genetic Changes and Post-translational Modification in the Protein Products of Specific Genes in Parkinson's Disease and in Substituted Amphetamine Neurotoxicity Using Quantitative Proteome Analysis in Mice Models and Human Subjects [Ali]	(1) To determine the post-translational protein modifications in the protein extracts of nigral and striatal tissues in substituted amphetamines and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice, (2) to evalulate the effect of various nNOS inhibitors and peroxynitrite decomposition catalysts on the post-translational protein modifications in the protein extracts of nigral and striatal tissues in mice treated with substituted amphetamines and (3) to determine protein-DNA interactions in nuclear extracts from nigral and striatal tissues in mice treated with substituted amphetamines and MPTP for the evaluation of novel post-translational changes in the proteins mediated by various transcription factor, (4) to determine the effect of various nNOS inhibitors on substituted amphetamine and MPTP-induced free radical production and monoamine concentrations in mouse brains, (5) to determine the nitrated protein on tyrosine hydroxylase by immunoprecipitation of tyrosine hydroxylase and co-localization of 3-nitrotyrosine in the presence and absence of nNOS inhibitors to correlate physiological effects with protein changes from objectives 1, 2 & 3, and (6) to determine the post-translational protein modifications in protein extracts and protein-DNA interactions in nuclear extracts of nigral and striatal tissues obtained from human subjects with Parkinson's Disease.
Effect of p53 Genotype on Gene-Expression Profiles in Mice Exposed to the Model Mutagen, N-ethyl-N'-nitrosourea (ENU) [Morris]	(1) To determine the effect of mutation in the p53 tumor suppressor gene on gene-expression profiles in young and aged mice and (2) to determine the effect of mutation in the p53 tumor suppressor gene on gene expression profiles in young and aged mice exposed to the model mutagen ENU.
Methods for Support of a Functional Proteomics Facility at NCTR [Yu]	(1) To establish and standardize for routine use procedures for whole cell and subcellular organellar isolation for a variety of tissues; (2) to develop and standardize specific and sensitive markers of cell type and organellar purity and yield; (3) to identify, adapt, develop, and standardize appropriate 2-D protein separation techniques; and (4) to integrate results of objectives 1-3 to provide "front-end" components of a functional proteomics facility.
Dietary Modulation of the Renal Toxicity of p-Nonylphenol and Di(2-ethylhexyl)phthalate (DEHP) [Delclos]	(1) To demonstrate that the cystic kidney disease previously shown to be induced by p-nonylphenol in developing NCTR CD rats fed a soy-free diet is decreased in incidence and/or severity in rats fed soy-containing diets; (2) to evaluate the renal toxicity of dietary DEHP in developing rats maintained on a soy-free diet; (3) to evaluate potential early markers of renal cystogenesis in p-nonylphenol- and DEHP-treated rats and their modulation by soy-containing diets; (4) to evaluate the roles of modulation of antioxidant defenses and cyclooxygenase activities in the protective effect of soy against p-nonylphenol and, if demonstrated, DEHP-induced renal toxicity; and (5) as secondary objectives in the above studies to assess the effect of diet on hepatic, testicular, and lung toxicity of DEHP.
Allele-specific Competitive Blocker (ACB) - Polymerase Chain Reaction (PCR) Measurement of Azoxymethane-induced Rat K-ras codon 12 GGT-->GAT and GTT-->GTT Mutations in Colonic Aberrant Crypt Foci Isolated using Laser Capture Microdissection [McKinzie]	(1) To use newly established PCR-based methods to quantify the rat K-ras codon 12 GGT ' GAT and GGT ' GTT mutant fractions in rat colonic mucosa, aberrant crypt foci, and tumors at specified times after colon tumor initiation by azoxymethane treatment and (2) to use these data in conjunction with K-ras mutant fraction data generated from studies of human colon to determine how rodent data can be extrapolated to human disease.
Analysis of p53 Codon 270 CGT to TGT Mutation in Simulated Solar Light (SSL)-induced Skin Tumors and Exposed Mouse Skin [Parsons]	(1) To develop the ACB-PCR detection of mouse p53 codon 270 CGT >TGT mutation, (2) to measure the frequency of detection and levels of this mutation in mouse skin tumors, (3) to measure the frequency of this mutation in skin tissue from tumor-bearing animals, and (4) to measure the frequency of this mutation in skin exposed to decreasing levels of SSL.
Measurement of Cancer-associated Gene Mutation in Colon Tumor and Nontumor Tissue [Parsons]	(1) To determine K-ras codon 12 GGT to GAT and GGT to GTT mutant frequencies in colonic aberrant crypt foci, adenomas, and carcinomas; first by DNA sequencing and, if mutation is not detected, then by ACB-PCR; (2) to determine K-ras codon 12 GGT to GAT and GGT to GTT mutant frequencies in tumor-margin samples and tumor-distant, normal-appearing colonic epithelium from colon cancer patients; and (3) to determine K-ras codon 12 GGT to GAT and GGT to GTT mutant frequencies in autopsy samples of colonic epithelium from colon disease-free individuals.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Assessment of Interindividual Variability in Expression of DNA Methyltransferases (DNMT), DNMT3a, and DNMT3b, in Liver and Identification of Factors Influencing Expressions [Hammons]	1) To determine levels of expression of DNMT3a and DNMT3b in liver samples from a pool of donors selected according to smoking status, gender, and age; (2) to determine the effect of tobacco smoke on DNMT1, 3a, and 3b expression in liver cell systems; and (3) to assess the polymorphism frequency identified in DNMT3b in the sample pool included in the study and assess whether it is correlated with expression.
Can Polymorphism in Human DNMT3b Potentially Affect Individual Responses to Xenobiotics and Chemopreventive Agents? [Hammons]	(1) To develop plasmid constructs with CC wildtype and TT homogenous variant of DNMT3b to examine transcriptional activity, (2) to use activity assays to compare transcriptional activity of gene constructs transfected into liver cells, and (3) to determine whether xenobiotics or dietary agents affect transcriptional activity differently in CC, CT or IT transfected cells.
Global and Locus-specific DNA Hypomethylation: A Common Mechanism Involved in Genotoxic and Non-genotoxic Rat Hepatocarcinogenesis [Pogribny]	(1) To determine if the temporal alterations in genomic methylation profile in preneoplastic liver tissue observed in the folate/methyl-deficient model of rat endogenous hepatocarcinogenesis also occur in other carcinogenesis models; (2) to identify genes that are consistently up-regulated or down-regulated in target tissue during the promotion stage of carcinogenesis; and (3) to evaluate whether the global and locus-specific DNA hypomethylation, along with aberrant expression of related genes and changes in chromatin conformation, is specific only to target tissues and if may be used for early detection of chemicals with carcinogenic potential.
Carcinogenicity of Acrylamide and its Metabolite Glycidamide in Rodents: Neonatal Mouse Bioassay [Beland]	To compare the carcinogenicity of acrylamide and its metabolite glycidamide in B6C3F1 mice treated neonatally.
Development of MitoChip, a Glass-based Oligonucleotide Microarray Containing Mitochondrial and Nuclear Genes Associated with Mitochondrial Function [Desai]	(1) To develop a MitoChip, a GeneChip Mitochondrial Resequencing Array, containing genes associated with mitochondrial function such as oxidative phosphorylation, B-oxidation of free fatty acids, tricarboxylic acid cycle, apoptosis, as well as genes involved in the replication, transcription, translation of mitochondrial DNA, DNA repair, and regulation of DNA copy number; (2) to validate the MitoChip by evaluating gene expression profiles of AZT, an anti-HIV drug, and 3-nitropropionic acid, neurotoxins known to alter mitochondrial function; and (3) to verify the relative expression levels of differentially expressed genes by real-time quantitative PCR.
Assessment of Ketamine in the Developing Nonhuman Primate [Wang]	(1) To determine, using neurohistochemical approaches, if, and at what developmental stages, ketamine exposure increases neuronal apoptosis/proliferation; (2) to determine, using neurohistochemical approaches, the dose-response for ketamine to produce apoptosis at the most sensitive developmental stage; (3) to determine the reversibility or permanence of the response using behavioral, imaging, and neurohistochemical approaches; and (4) to determine, at the most sensitive stage and dose, genomic and proteomic responses to ketamine treatment.
Preclinical Metabonomic Biomarkers of Toxicity and Disease [Beger]	To examine the utility of metabonomics as an approach to produce predictive models of cardiovascular, renal, neural, and hepatic toxicity. The models will be built using a variety of pattern-recognition technologies to determine how temporal endogenous metabolic changes found in nuclear magnetic resonance (NMR) and/or mass spectrometry (MS) spectra of urine, serum, and tissue are related to toxicity and disease state.
Phosphatidylinositol Glycan - Complementation Group A (PIG-A) Mutagenesis: Development of Methods for the Identification and Molecular Characterization of Mutations in the PIG-A Gene in Human Lymphoblastoid Cells and C57Bl/6 Mice [Dobrovolsky]	(1) To develop flow-cytometric methods for the detection of cells with mutations in the PIG-A gene using wild-type and mutant human lymphoblastoid cells, TK6, and WTK1, as a model and (2) to develop flow cytometric methods for the detection of hematopoietic cells with mutations in the PIG-A gene in C57Bl/6 mice.
PIG-A Mutagenesis: Development of Methods for the Identification and Molecular Characterization of Mutations in the PIG-A Gene of F344 Rats [Heflich]	(1) To develop methods for measuring PIG-A mutant frequencies in lymphocytes cultured from rats, (2) to develop flow cytometric methods for measuring PIG-A mutant/variant frequencies in both the lymphocytes and red blood cells of rats, (3) to treat rats with either ENU or 7,12-dimethylbenz[α]anthracene and measure PIG-A mutant manifestation in lymphoctyes and compare results with PIG-A variant manifestation in red blood cells and Hprt mutant manifestation in lymphocytes, and (4) to determine the spectra of the PIG-A and Hprt mutations induced in the mutant lymphocytes detected in Objectives 1, 2 and 3.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Phytoestrogens and Aging: Dose, Timing, and Tissue [Doerge]	(1) To evaluate the potential benefits or detrimental effects of dietary phytoestrogens on breast cancer progression, adipose tissue, and the brain, using well-established laboratory animal models and (2) to complete additional studies to determine bioavailability of soy isoflavones in neonatal and adult male non-human primates.
Development of a Physiologically-based Pharmacokinetic/Pharmacodynamic (PBPK/PD) Model for Acrylamide [Doerge]	(1) To develop a PBPK/PD model for acrylamide and glycidamide, (2) to determine the mutagenicity of acrylamide and its metabolite glycidamide in Big Blue rats, and (3) to determine the DNA adduct levels and the extent of mutagenicity of furan and its metabolite cis-2-buten-4-dial in neonatal B6C3F1/Tk+/- mice.
Development of Liver Toxicity Knowledge Base (LTKB) to Empower the FDA Review Process [Tong]	To develop a Liver Ontology that characterizes liver pathology and toxicity. The ontology will be used as guidance for data collection/curation, classification and analysis with the following specific aims: (1) gene expression data – the primary data collected for this project will be existing gene expression data. Other types of data such as data from proteomics, metabonomics, and genotyping studies (including genome-wide association studies) will be considered as the project progresses. (2) text mining – NCTR will conduct text mining on >13 million abstracts in PubMed and other public resources with an emphasis on liver-related data. The association between the liver-specific entities (i.e., genes/proteins, pathways, drugs, tissues and toxicity) will be established. (3) known data – there is substantial knowledge available in public domains on liver toxicity, including genes/proteins (e.g., signatures and biomarkers), pathways/networks, and chemicals/drugs. NCTR will assemble this knowledge in such a way that it can be integrated with other information in LTKB and effectively mined. (4) experiment – NCTR will conduct gene expression studies on well understood and characterized hepatic and non-hepatic compounds. The dataset will be used to validate the LTKB. Data from 50 compounds will be generated in the first year of this project and will serve as proof of principle. Data for 150 additional compounds will be collected in the following two years, assuming the first set of data supports the LTKB approach. (5) LTKB - the data/information generated from the specific aims will be analyzed (combined and correlated) to establish liver toxicity-related regulatory networks and genes/proteins-pathways-chemicals-disease associations. A set of training rules will be identified to minimize the false positives in LTKB.
Evaluation of the Genetic Toxicity and Behavioral Effects of Chronic Methylphenidate Exposure in Juvenile Male Rhesus Monkeys *(Macaca mulatta)* [Morris]	(1) To determine the baseline frequency of measures of genetic damage in a population of juvenile rhesus monkeys, (2) to determine the frequency of these measures of genetic damage in a population of juvenile rhesus monkeys at defined intervals during a chronic exposure to methylphenidate, (3) to determine if chronic exposure to methylphenidate results in measurable effects on the behavior of juvenile rhesus monkeys utilizing the NCTR Operant Test Battery, and (4) to determine the plasma concentration of methylphenidate and its major metabolite ritalinic acid during the chronic exposure of juvenile rhesus monkeys to the drug.
Detection of DNA Adducts in Mice Treated with Benzo[a]pyrene at Low Exposure Levels [Fu]	To define dose-response curves for benzo[a]pyrene DNA adducts in the A/J mouse lung, utilizing the application of HPLC-ES-MS/MS methodologies developed at NCTR.
Biotransformation of Isoflavonoid Phytoestrogens by Colonic Microfloras of Experimental Animals [Rafii]	To use fecal samples of monkeys and rodents to determine if the metabolites produced by intestinal microfloras of experimental animals exposed to phytoestrogens are the same as those of humans or whether the animal-colonic bacteria metabolize them to different compounds. This information is necessary for extrapolation to humans of the data obtained from treatment of animals with phytoestrogens.
Molecular Mechanisms Underlying Gender-associated Differences in the Adverse Reactions to the Antiretroviral Agent, Zidovudine (AZT): Role of Mitochondrial Toxicity [Desai]	To elucidate molecular mechanisms of mitochondrial dysfunction that will address gender-based differences in adverse effects of antiretroviral drugs such as AZT. This will provide critical information to the FDA for development of guidelines to plan new treatment strategies to reduce the frequency and severity of antiretroviral-related toxic effects in women, particularly in pregnant women.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Neurotoxicity Assessment of Manganese (Mn) Nanoparticles in PC12 Cells and in Mice [Ali]	(1) To evaluate the neurotoxicity of different size Mn nanoparticles using PC 12 cultured cells; (2) to determine if *in vitro* exposure to Mn nanoparticles selectively induces specific genomic changes in PC12 cultured cells using oligonucleotide microarrays; (3) to determine if multiple doses of Mn nanoparticles produce ROS, alterations in lipid peroxidation and/or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase), and levels of glutathione in various regions of the mouse brain; (4) to determine if single or multiple doses of Mn nanoparticles induce specific genomic changes in various regions of the mouse brain using oligonucleotide microarrays; (5) to determine if single or multiple doses of Mn nanoparticles produce significant changes in neurotransmitter concentrations in various regions of the mouse brain; and (6) to determine if single or multiple doses of Mn nanoparticles produce significant changes in the formation of 3-nitrotyrosine, an *in vivo* biomarker for oxidative stress, in various regions of the mouse brain.
Methods Development for High-resolution Dedicated Positron Emission Tomography (microPET) to Rodent Neuroplasticity and Toxicity During Development [Wang]	Advances in pediatric and obstetric surgery have resulted in an increase in complexity, duration, and number of anesthetic procedures. To understand the effects of anesthetic drugs on the developing nervous system and to minimize risks to children resulting from the use of anesthesia, this study will utilize microPET to screen and evaluate *in vitro* and *in vivo* measurements from a broad range of pathophysiological or pharmacological parameters using specific tracers in the developing rat. Three different age groups of developing rats will be used: pregnant day 18 female rats, postnatal day 7 rat pups, and postnatal day 35 rats. This study will also attempt to elucidate the relationship between apoptosis-identifying ligands (specific tracers) and subsequent behavioral deficits.
Cancer Mutations as Biomarkers of Cancer Risk: Human Studies with Implications for Personalized Medicine [Parsons]	(1) To develop the information necessary for the rational use of oncogene mutations as quantitative biomarkers of cancer risk using ACP-PCR to determine normal and pathological levels of relevant oncogene mutations in multiple human tissues and tumors; (2) to compare the information derived from human tissues with data generated in a parallel rodent protocol as an approach for incorporating carcinogenesis-relevant data into the rodent to human extrapolation necessary in cancer risk assessment; (3) to validate a streamlined ACP-PCR methodology and develop the methodology necessary to measure oncogene mutation frequency in cell-free DNA isolated from plasma; and (4) to convey to the regulatory risk-assessment community, through a series of publications, the regulatory significance of the data regarding tumor-associated mutations which have and will be generated.
Liver Toxicity Biomarkers Study: Phase 1, Entacapone and Tolcapone [Beland]	To establish liver toxicity biomarkers and associated algorithms for use in preclinical drug development that will predict the probability of occurrence of hepatocellular injury at any subsequent phase of drug development or following approval of the drug for marketing. Emphasis will be placed upon drugs that do not demonstrate "classical" signs of liver toxicity during preclinical stages of drug development.
Development of a New Safety Evaluation Method Using MicroRNA (miRNA) Expression Analysis as a Biomarker for Detecting Carcinogens [Chen]	(1) To determine miRNA expression profiles of the tumor target tissues of rats and mice treated with genotoxic carcinogens AA, riddelliine, and comfrey; and non-genotoxic carcinogens, propiconazole, and triadimeforn, as well as non-carcinogen myclobutanil using microarray technologies; (2) to develop a PCR array containing the primers that are specifically used to amplify carcinogensis-related miRNAs and use the PCR array to conduct time-course and dose-response studies for miRNA expression alterations in tissues of rats treated with carcinogens; and (3) to define the miRNA biomarker genes that are associated with carcinogen exposure by prediction of their target genes and determination of their biological functions.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Neurotoxicity Assessment of Silver (Ag) Nanoparticles in PC-12 Cells and in Rats [Ali]	(1) To evaluate the neurotoxicity of different sizes of Ag nanoparticles using cultured PC12 cells; (2) to determine if *in vitro* exposure to Ag nanoparticles selectively induces specific genomic changes in cultured PC12 cells using microarrays; (3) to determine if single or multiple doses of Ag nanoparticles produce ROS, alterations in lipid peroxidation, and/or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) and glutathione levels in the rat brain; (4) to determine if single or multiple doses of Ag nanoparticles induce specific genomic changes in the rat brain as indicated with microarrays; (5) to determine if single or multiple doses of Ag nanoparticles produce significant changes in neurotransmitter concentrations in the brain in rat; (6) to determine if single or multiple doses of Ag nanoparticles produce significant changes in the formation of 3-nitrotyrosine, an *in vivo* biomarker for oxidative stress, in the rat brain; and (7) to determine if multiple doses of Ag nanoparticles produce morphological alterations in the blood-brain barrier, brain, or other visceral organs of the rat.
Development of High Throughput Methodology for Detection of *In Vivo* Mutation in the Endogenous PIG-A Gene of Human Blood Cells Using Flow Cytometry [Dobrovolsky]	(1) To design high throughput methods for detecting PIG-A mutant human red and white blood cells by flow cytometric detection of cells lacking cell surface protein markers anchored by glycosyl phosphatidyl inositol (e.g., CD59, CD48); (2) to use the methods developed in Objective 1 to establish a normal range of PIG-A mutant frequencies in red and white blood cells and compare these ranges with those of different groups of human subjects hypothesized to have increased mutational loads. The groups will include, but will not be limited to (a) patients with the disease paroxysmal nocturnal hemoglobinurea, (b) patients undergoing radiation treatment or chemotherapy with DNA reactive drugs, and (c) patients predisposed to cancer due to inherited deficiencies in endogenous pathways; and (3) to compare, when the volumes of blood samples permit, red blood cell PIG-A mutant frequencies determined in Objective 2 with PIG-A mutant frequencies in white blood cells from these samples determined by limiting-dilution cloning, and to determine the PIG-A DNA sequence changes reponsible for the white blood cell mutants.
Evaluation of the Ability of Both the Agar and Microwell Versions of the MLA to Optimally Detect the Mutagenic Potential and Potency of Complex Chemical Mixtures [Moore]	To develop science-based best practice standard and tools to incorporate translational and applied toxicological advancements into the regulatory science process to create a seamless bench-to-bedside continuum.
Assessment of Gaseous Anesthetics in the Developing Nonhuman Primate [Wang]	(1) To evaluate dose-response effects of gaseous anesthetics to determine if prolonged exposure to nitrous oxide or isoflurane alone will result in an increase in neuronal cell death and to determine if combinations of nitrous oxide and isoflurane will prevent or enhance each other's effects on the developing nonhuman primate; (2) to determine if a relative high dose or prolonged exposure of developing nonhuman primates to nitrous oxide or isoflurane alone or in combination will induce long-term behavioral deficits, as well as long-lasting pathological changes; (3) to determine, using noninvasive imaging techniques [microPET and magnetic resonance imaging (MRI)], if a high dose or prolonged exposure of developing nonhuman primates to nitrous oxide or isoflurane alone or in combination will induce long-lasting pathological changes. MRI will be used to verify pathological evidence and look for volume changes. MicroPET will be used to examine the sensitivity for tracing low picomolar concentrations of radiolabeled molecules, which is useful for studying dynamic imaging in animal models of human diseases; and (4) to identify potential underlying mechanisms that could link alteration of mitochondrial function and elevation of ROS to gaseous anesthetic-induced neuronal cell death. L-carnitine will be used to attenuate neurological brain injury associated with mitochondria-related degenerative effects induced by gaseous anesthetics in the developing nonhuman primate.
Evaluation of Growth and Pubertal Development In Male Rhesus Monkeys *(Macaca mulatta)* Chronically Exposed to Methylphenidate Hydrochloride (MPH) [Salminen]	To evaluate changes in pharmacokinetics and operant behavior testing in male monkeys chronically exposed to MPH. The initial experiment was designed to examine the genetic toxicity associated with chronic MPH treatment. This project will begin after the completion of the genetic toxicity experiments, to avoid procedures that could compromise those genetic toxicity data, specifically anesthesia and x-ray radiation.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Development of Methods for Evaluating DNA Damage using Single Cell Gel Electrophoresis (Comet Assay) in Rodents [Aidoo]	To evaluate and establish methods and conditions that enhance the sensitivity and reproducibility of the *in vivo* alkaline-comet assay for use in preclinical hazard identification and genotoxicity testing of food ingredients and chemicals for regulatory purposes.
Laboratory Studies in Melamine and Cyanuric Acid Biochemical Toxicology [Tolleson]	To determine chemical and biochemical properties of melamine and cyanuric acid that may influence their toxicity and retention as tissue residues.
Characterizing the Amphetamine-Induced Changes in Vascular Tone, Vasotrauma and Alterations in Angiogenesis in Rodent Brain [Bowyer]	(1) To evaluate the effects of both acute and chronic amphetamine (AMPH) exposure on the vasculature of the rat brain; (2) to examine vasculature within the parenchyma of three brain regions: the striatum, parietal cortex, and the combined piriform and amygdaloid nuclear cortices where AMPH-induced neurodegeneration can occur; (3) to observe the effects of AMPH on the vasculature associated with pial and arachnoid membranes (part of the meninges) and vasculature of the choroid plexus; and (4) to determine the alterations in AMPH-induced vascular gene expression after (a) 1-day, 4-dose exposure that produces hyperthermia [full time course of effects, not just first day], (b) a single exposure to a very high dose, (c) 9-day exposure that does not produce significant hyperthermia, and (d) 1-month exposure to AMPH included in the drinking water.
Chemical Inactivation of Protein Toxins on Food Contact Surfaces [Tolleson]	(1) To identify cleaning/sanitizing treatments that result in elimination and/or inactivation of protein toxins (abrin and ricin) on food contact surfaces, (2) to identify surrogate(s) that can be used to study chemical inactivation of abrin or ricin, and (3) to measure the loss of ricin and abrin biological and biochemical activities in the presence of cleaning/sanitizing solutions using RAW264.7 macrophage cytotoxicity assays and 28S rRNA adenosine N-glycosidase RTqPCR-based enzyme assays.
Method Development for Study of Antioxidant Properties in Dietary Supplements [Fu]	**Microsomal Metabolism-Mediated Studies:** (1) To determine whether or not the studied herbal dietary supplements can enhance or inhibit free radical formation, mediated by microsomal metabolism, in a dose-dependent manner and (2) to determine whether or not the studied herbal dietary supplements can enhance or inhibit microsomal metabolism-mediated lipid peroxidation in a dose dependent manner. **Cell Culture Studies:** (1) To determine the toxic effects, including mitochondrial dehydrogenase activity, intracellular ROS concentration, and mitochondrial membrane potential, of the studied herbal dietary supplements in cells, including A549 human lung carcinoma cells and rabbit brain rBCECs cells (a normal cell line to assay the toxic effect on the CNS) and (2) to determine, by use of the ESR oximetry technique, the inhibition/induction of lipid peroxidation by the studied herbal dietary supplements in A549 human lung carcinoma cells and rabbit brain rBCECs cells.
Use of Electron Spin Resonance (ESR) Spectroscopy to Characterize the Interactions Between Nanoscale Materials and Model Biological Systems [Fu]	**Chemical Reactions:** (1) To determine whether or not nanomaterials can catalyze a Fenton reaction to initiate hydroxyl radical formation in a nanoparticle size dependent manner and (2) to determine whether or not nanomaterials and/or their cations can be reduced by natural reducing agents, such as ascorbic acid and glutathione, leading to the formation of ROS. **Microsomal Metabolism-Mediated Studies:** (1) To determine whether or not nanomaterials enhance or inhibit free radical formation, mediated by microsomal metabolism, in a nanoparticle size-dependent manner and (2) to determine whether or not nanomaterials and/or their cations can enhance or inhibit microsomal metabolism-mediated lipid peroxidation in a nanoparticle size-dependent manner. **Cell Culture Studies:** (1) To determine the toxic effects, including mitochondrial dehydrogenase activity, intracellular ROS concentration, and mitochondrial membrane potential, of nanomaterials of different particle size in cells, including A549 human lung carcinoma cells and rabbit brain rBCECs cells (a normal cell line to assay the toxic effect on CNS) and (2) to determine, by use of the ESR oximetry technique, the inhibition/induction of lipid peroxidation by nanomaterials of different particle size in A549 human lung carcinoma cells and rabbit brain rBCECs cells.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Evaluation of the Applicability of Standard Assays for Assessing Genotoxicity of Engineered Nanomaterials [Chen]	(1) To assess the genotoxicity of four types of nanoscale materials, carbon nanotubes, nanoscale titanium dioxide, nanoscale gold, and nanoscale silver in three standard tests suggested by the FDA, *Salmonella Ames* test, mouse lymphoma assay, and *in vivo* mouse micronucleus assay and (2) to evaluate the possible mechanisms of nanomaterial-induced genotoxicity using a transgenic mutation system, comet assay, and genomic analysis.
Neurotoxicity Assessment of Carbon Nanotubes (CNTs) and Gold Nanoparticles using a Brain Microvascular Endothelial Cell System, PC12 Cultured Cells, and a Whole Animal Model (Rats or Mice) [Ali]	(1) To evaluate the neurotoxicity of single and multiple-wall and different sizes of CNTs using brain microvascular endothelial and PC12 cultured cells; (2) to determine, using microarrays, if the *in vitro* exposure to these CNTs (single and multiple walls) would selectively induce specific genomic/proteomic changes in brain microvascular endothelial and PC-12 cultured cells; (3) to determine if acute or chronic exposure of CNTs would produce ROS, alterations in lipid peroxidation and/or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) and glutathione levels in mouse brain; (4) to determine if acute or chronic exposure of CNTs would induce specific genomic/proteomic changes in mouse brain as indicated with microarrays; (5) to determine if acute or chronic exposure of CNTs would produce significant changes in neurotransmitter concentrations, formation of 3-nitrotyrosine, an *in vivo* biomarker for oxidative stress, in mouse brain; and (6) to determine if acute or chronic exposure of CNTs would produce morphological alterations in the brain or visceral organs of the mice.
Effect of Urinary pH upon the Nephrotoxicity of a Combined Exposure to Melamine and Cyanuric Acid [Beland]	To determine the effect of urinary pH upon the renal toxicities elicited by a combined exposure of melamine and cyanuric acid.
Assessment of the Nephrotoxicity of a Seven-day Combined Exposure to Melamine and Cyanuric Acid [Gamboa da Costa]	To investigate the nephrotoxic effect of a seven-day co-exposure to melamine and cyanuric acid in Fischer 344 rats.
Methylphenidate (Ritalin) Exposure during Pregnancy: Assessment of Neurotoxicity in Offspring [Ferguson]	(1) To quantify the neurobehavioral toxicity associated with pre- and early postnatal treatment with methylphenidate in rats; (2) to evaluate a wide range of behaviors at preweaning, adolescent, and adult ages to fully describe the potential effects; and (3) to evaluate the hypothesis that, at human-relevant serum levels of methylphenidate, alterations in baseline locomotor activity as well as locomotor response to a later methylphenidate challenge may be produced, and that higher doses will produce more significant effects.
Biomarkers of Liver Toxicity [Salminen]	(1) To discover biomarkers of hepatotoxicity in preclinical studies that are more predictive of adverse effects in humans [these biomarkers may or may not be directly applicable to the clinic, but they must be predictive of human responses so that they can be used to extrapolate preclinical data to humans in safety assessment] and (2) to publish and make the biomarkers publicly available to fulfill FDA's goal of developing science-based best practice standards, guidance, and tools to improve the regulatory processes. Farther-reaching goals include the qualification of such biomarkers (e.g., via the FDA/ European Medicines Agency qualification process) and potential translation for clinical use.
Development of Predictive Mitochondrial Biomarkers for Drug-induced Cardiotoxicity Using a System Biology Approach [Desai]	(1) To perform non-invasive measurements of heart rate, heart rate variability, and electrocardiogram using ECGenie™; (2) to measure cardiac troponin T, creatine kinase MB, and cardiolipin levels in plasma as indicators of doxorubicin-induced cardiac tissue damage; (3) to identify morphological changes in cardiac mitochondria in the left ventricular region by electron microscopy; (4) to use "omics" technologies for analyte profiling in the heart, transcriptional profiling of approximately 906 mitochondria-related genes using MitoChip, protein profiling by 2D-HPLC/MS/MS, and measurement of endogenous metabolites by nuclear magnetic resonance (NMR) and MS; (5) to measure expression levels of 906 mitochondria-related genes in whole blood using MitoChip; (6) to measure levels of creatinine, creatine, lactate, Krebs cycle intermediates, and small ketone bodies in plasma using metabolomics; and (7) to integrate genomic, proteomic, and metabolomic endpoints in the heart tissue to define the molecular basis of doxorubicin-induced cardiac toxicity and to correlate "omics" data to genomic findings obtained in whole blood.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Development of an FDA Resource and Knowledge Base for Sex Difference in Drug-Induced Liver Injury (DILI) [Tong]	(1) To develop a knowledge base for the sex differences in DILI through analyzing , and modeling the molecular data in public domain; (2) to further augment the collection of the genomic data from public resources and through collaborations; (3) to develop a standard data curation model for the sex-biased DILI in ArrayTrack to manage the collected data [the data curation model will be developed in accordance with the data standard developed in FDA for electronic data submission]; (4) to conduct the meta-analysis, text mining, and network analysis to develop a relationship between drugs, molecular signatures, liver-specific biomarkers, genes/proteins functions, pathways and sex-biased liver toxicity; (5) to gain understanding, at molecular level, of sex-biased differences in DILI; and (6) to provide knowledge and resources from this project for the FDA to utilize and reference when sex-related DILI issues arise during the various stages of the regulatory review process, thus impacting women's health.
Collaborative Inter-agency Development of *In Silico* Computational Toxicology Modeling to Predict Adverse Drug/Chemical Interactions with Cytochrome p450 Enzymes [Beger]	(1) To develop *in silico* computational models to predict chemical interactions that can inhibit CYP3A4 and CYP2D6 enzymes, (2) to have each government agency build and test a different type of *in silico* computational model to predict chemical interactions that can inhibit these enzymes, and (3) to use several different modeling methods to model compound-compound-enzyme interactions because no modeling technique is perfect and each technique has strengths and weaknesses compared to other modeling techniques. NCTR will build structure-activity relationship (SAR) and spectrometric data-activity-relationship (SDAR) models of chemical interactions that inhibit CYP3A4 and CYP2D6 enzymes. CDER will build predictive quantitative SAR (QSAR) models with a training set of drugs and chemicals that inhibit CYP3A4 and CYP2D6 reversibly and irreversibly. ATSDR will build docking models of chemicals that contaminate drinking water and interact with CYP3A4 and CYP2D6 enzymes. These *in silico* models will be built with chemicals that have been reported to inhibit these P450 enzymes. Some of the chemicals used to form these models have been found in drinking water so these interactions could happen without polypharmacy. Cytochrome CYP3A4 and CYP2D6 are two of the major phase I drug metabolizing enzymes and drugs or chemicals that inhibit them could alter drug pharmacokinetics and associated drug toxicity or drug efficacy endpoints. Understanding these drug-enzyme inhibitory interactions and having the ability to accurately predict these interactions should drastically improve drug safety evaluation and increase protection of public health.
3D- and 4D-QSDAR Modeling Applied to Various Toxicological Endpoints [Beger]	(1) To develop 3D- and 4D-QSDAR models for endocrine disruptors, lowest-observed-adverse-effects level (LOAEL), and no observed-adverse-effects level (NOAEL), and other relevant toxicological endpoints; (2) to test the training models with external test sets and compare the training and testing results to previous QSDAR, quantitative structure-activity relationship (QSAR), and SAR models; and (3) to determine how the technique can be used to predict how 13C or 15N NMR spectra affects 3D-QSDAR modeling.
Relationship between Liver Epigenetic Phenotype and Susceptibility to Nonalcoholic Steatohepatitis (NASH)-induced Hepatocarcinogenesis in Mice [Pogribny]	(1) To determine the role of epigenetic dysregulation in the etiology and pathogenesis of dietary NASH-induced hepatocarcinogenesis in mice, 2) to determine whether or not interstrain-specific susceptibility of mice to NASH-induced hepatocarcinogenesis is associated with differences in individual hepatic epigenetic phenotypes, (3) to determine the role of epigenetic dysregulation in the etiology and pathogenesis of NASH-induced hepatocarcinogenesis in mice induced by tamoxifen administration, and (4) to determine whether or not aberrant epigenetic markers can be used as targets for prevention of NASH-induced hepatocarcinogenesis in mice.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Methods Development for Toxicity Assays using the Zebrafish Embryo as a Model System: Whole Animal High Throughput Assays for Chemical Testing [Kanungo]	(1) To establish a high throughput assay system using zebrafish embryos for toxicity assessments of FDA relevant compounds; (2) to monitor both traditional morphological and behavioral endpoints of toxicity and the newer, more subtle organ-specific toxicities; (3) to study the effect of methamphetamine on zebrafish embryos, especially relating to sensory and motor neuron development; 4) to determine if carbon nanotubes pass through the blood brain barrier in zebrafish embryos and have any toxic effects on early development; (5) to determine whether these nanomaterials generate ROS, cause the depletion of dopamine and its metabolites, dihydroxyphenylacetic acid and homovanillic acid, and alter markers of oxidative stress; and (6) to study the effect of nicotine on zebrafish embryos, especially relating to sensory and motor neuron development and the mechanism of action.
Long-term Consequences of Neonatal Ketamine Anesthesia in Rhesus Monkeys: Extended Congnitive Assessments [Kanungo]	(1) To continue monitoring the cognitive capabilities of rhesus monkey subjects exposed to a single, 24-hour bout of ketamine-induced anesthesia during the first week of life and (2) to extend the functional domains that are being assessed to include performance of a temporal discrimination task (timing task), a counting task, and reversal learning tasks (cognitive flexibility). Data to date indicate that, compared to control animals, ketamine-exposed subjects exhibit significant deficits in several aspects of brain function including learning, the ability to perform simple visual discriminations, motivation and speed of psychomotor processing. Continuing these observations will provide valuable information on the ultimate time course and severity of the observed deficits.
Pharmacokinetics of Aurimune (NCL74) and Docetaxel (Taxotere) in Nonhuman Primates [Matson]	(1) To conduct pharmacokinetic studies for various Nanotechnology Characterization Laboratory-supplied nanomaterials in nonhuman primates and (2) to perform measures of toxicity, specifically immunotoxicity, that are amenable to blood analyses (e.g., clinical chemistries, hematology, complement activation, and cytokine profiles).
Assessing Acetaminophen-induced Liver Injury and the Influence of Dietary Supplements – Potential Synergistic Interactions [Salminen]	(1) To identify acetaminophen-dietary supplement interactions to allow warnings to be provided to women and better assessment of the safety of the current therapeutic uses of acetaminophen and the protection afforded by the U.S. dietary supplement regulations, (2) to identify differential sex-sensitivity to acetaminophen in combination with dietary supplements, and (3) to analyze biological pathways that are affected by the dietary supplements and acetaminphen individually and when combined to provide insight into the mechanism(s) of the interaction and why females are more sensitive to acetaminphen DILI.
Quality Control (QC) for Focused and Unfocused LC-MS-based Metabolomic Profiling of Blood Samples [Bhattacharyya]	(1) To develop and test a QC protocol on existing preclinical hepatotoxicity protocols (acetaminophen-induced injury and the influence of dietary supplements; liver toxicity biomarkers) that can potentially be translated to clinical metabolomics experiments that are planned and (2) to test the hypothesis that adding QC will improve both intra-lab and inter-lab reproducibility of LC-MS-based metabolomics of blood samples.
Assessment of Iron Oxide Nanoparticle-induced Neurotoxicity in Cell Cultures and Whole Animal Models [Binienda]	(1) To determine if acute or chronic exposure of different sizes to iron oxide nanoparticles produces specific changes in the mitochondrial function, cell death, and generation of ROS in different regions of rat and mice brain using *in vivo* microdialysis, (2) to determine if acute or chronic exposure to iron oxide nanoparticles produces significant changes in neurotransmitter concentrations in different regions of mice/rat brains using microdialysis, (3) to determine if acute or chronic exposure to different sizes of iron oxide nanoparticles produce alterations in the brain free fatty acid levels, (4) to determine if acute or chronic exposure to different sizes of iron oxide nanoparticles produces alterations in lipid peroxidation and/or changes in antioxidant enzyme activity (catalase, superoxide dismutase, glutathione peroxidase) and glutathione levels in mice and rat brains, and (5) to determine if acute or chronic exposure to different sizes of iron oxide nanoparticles produces selective patterns of deposition and damage in different regions of rat and mice brain using *in vivo* MRI.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Development and Application of a Mitochondria-specific Gene Array (MitoChip) for the Investigation of Clinical and Non-clinical Predictive Biomarkers of Toxicity [Desai]	(1) To develop MitoChips for various mammalian species, including rat, non-human primate, and human; (2) to perform transcriptional profiling of mitochondria-related genes using mitochondria-specific gene arrays to investigate the mechanisms of drug toxicities and degenerative diseases associated with mitochondrial dysfunction in different mammalian species; and (3) to characterize species-specific transcriptional profiles to predict risk of drug toxicity or disease onset in different mammalian species.
Evaluation of Transgenic gpt-delta Mice developed at NCTR Breeding Colony for Detecting Point Mutations and Large Deletions [Manjanatha]	(1) To dose by gavage daily for 28 days groups of gpt-delta transgenic mice (8B-NCTR Breeding colony) with low, intermediate, or high doses of cyclophosphamide, bleomycin, and 100 mg/kg ENU [as a positive control for induction of mutations in the transgenes gpt, red, and gam (spi- selection)]; (2) to characterize recovered mutants from target tissues for generation of gpt and spi mutational spectra; and (3) to analyze red blood cells for PIG-A mutant frequencies and erythrocytes for micronucleus frequencies, respectively.
In Vitro Assay to Predict Developmental Neurotoxicity of Pediatric Anesthetics [Wang]	(1) To use rodent *in vitro* organotypic and primary culture models to examine anesthetics including propofol (gamma-aminobutyric acid [GABA] A agonist), baclofen (GABA B agonist), diazepam (GABA A agonist), pentobarbital (GABA A agonist & 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl)propanoic acid) antagonist), etomidate (GABA A agonist), sevoflurane (N-methyl-D-aspartic acid [NMDA] antagonist & GABA agonist), fentanyl (opiate agonist), and anesthetic combinations commonly used in pediatric surgical procedures; (2) to determine the utility of *in vitro* culture systems to predict *in vivo* outcomes in subsequent studies; (3) to determine the dose and time-course over which the potential neurotoxic effects of anesthetics are expressed in the developing brain; (4) to determine effective ways to protect against anesthetic-induced developmental neurotoxicity that have potential clinical utility; (5) to identify mechanisms that link altered NMDA receptor function and/or elevation of ROS to anesthetic-induced neuroapoptosis; and (6) to identify biomarkers such as genomic pathway signatures and determine their validity for predicting *in vitro* outcomes of pediatric anesthetic exposure.
PIG-A mutagenesis: an International Validation Study Comparing PIG-A Mutation in Rats with Other Biomarkers of Genetic Toxicity [Heflich]	(1) To generate data using a standardized protocol that, in combination with results from other investigators, will be used to determine the sensitivity, specificity, and portability of the rat red blood cell/reticulocyte (RBC/RET) PIG-A gene mutation assay and (2) to perform the *in vivo* Comet, MN, and PIG-A and Hprt lymphocyte gene mutation assays in conjunction with the RBC/RET PIG-A assay to determine how the RBC/RET PIG-A assay compares in terms of sensitivity and specificity with these other *in vivo* assays that have been used or considered for use as regulatory assays.
Development of a High Throughput Assay for Measuring *In Vivo* Mutation in an Autosomal Gene [Bhalli]	(1) To develop a high throughput *in vivo* mutation model that detects mutations induced by a range of mechanisms, including gene mutation, large deletions, and loss of heterozygosity, and (2) to evalute the basic properties and sensitivity of the model in experiments employing well-characterized mutagens.
Effect of Soy-containing Diets on Ammonium Perchlorate-induced Thyroid Toxicity in Sprague-Dawley (SD) Rats - II [Doerge]	To determine the effect of dietary whole soy and purified genistein, the principal soy isoflavone, on the dose-response characteristics for perchlorate-induced thyroid toxicity in male SD rats. The results from the previous study, while incomplete and therefore insufficient to inform regulatory policy, largely substantiate the original hypothesis that soy diets can adversely affect thyroid function in the presence of additional risk factors.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
PBPK Models for Bisphenol A (BPA) [Fisher]	(1) To create PBPK models for BPA in three species of adult, neonatal, and pregnant (mother and fetus) and lactating (mother and neonate) laboratory animals (mouse, rat, and rhesus monkey); (2) to use these PBPK models to calculate internal measures of dose for both aglycone (i.e., active) and conjugated (i.e., inactive) forms of BPA; (3) to create human PBPK models for BPA (adult, child, and pregnant mother and fetus, and lactating mom and infant) using information obtained from the monkey, mouse, and rat, and limited information from the human published in the literature; (4) to use the human suite of PBPK models to extrapolate the internal doses of BPA associated with toxicity in laboratory animals to humans and to extrapolate dosimetry from regions of observation to low levels of exposure to BPA for which no experimental data exist; (5) to use this simulation protocol to help reduce the uncertainty in the assessment of health risks posed by BPA to human populations; (6) to use the human BPA PBPK model to help interpret biomonitoring data for BPA in urine and blood [the type of modeling is called reverse dosimetry]; (7) to consider a biologically-based dose response (BBDR) model for BPA, depending on the emerging knowledge about mode of action research for relevant adverse health effects; and (8) to propose for follow-on modeling beyond 3 years of this work to describe the interaction of BPA at target organs.
BPA Neurobehavioral Studies [Ferguson]	To establish the appropriate skills and techniques, which include complex behavioral assessments and quantitative volumetric analysis of sexually dimorphic brain regions, for the conduct of developmental toxicity studies with BPA.
DNA Methylation is Modulated by Lifestyle Factors and Environmental Agents [Word]	(1) To determine the effect of cigarette smoke condensate on DNA methylation of several genes in lung cells, and (2) to assess the ability of other agents to modulate the effect of class-specific correlations on gene DNA methylation, either singularly or in various combinations.
Impact of Melamine on Human Intestinal Microbiota: Does the Human Intestinal Microbiota have the Enzymatic Capacity to Metabolize Melamine to Cyanuric Acid? [Cerniglia]	(1) To determine if melamine impacts the population dynamics of the human intestinal microbiota, and (2) to determine if the human intestinal microbiota metabolize melamine to cyanuric acid.
NCTR/ Arkansas Regional Laboratory/ Office of Regulatory Affairs Nanotechnology Core Facility	(1) To support the needs of NCTR to characterize nanoscale materials used in toxicology tests and to detect these materials in biological samples and (2) to support the needs of Arkansas Regional Laboratory/Office of Regulatory Affairs to detect and characterize nanoscale materials in FDA-regulated products.
Analytical Assay for Photochemical Generation of Hydroxyl Radical [Howard]	(1) To provide support for analysis of the photoactivation of nanomaterials using the OH/coumarin-3-carboxylic acid assay, (2) to provide particle-size analysis for all materials being analyzed by the OH method and other nanomaterials used in studies at NCTR and Arkansas Regional Laboratory/Office of Regulatory Affairs, and (3) to improve the assay using ultraviolet light diode laser (on hand) as a replacement for the existing broad band ultraviolet light A source.

**Funded by NCTR voluntary allocations*

NIEHS/NTP

NIEHS/NTP staff at the NIEHS building, Research Triangle Park, NC

Photo courtesy of Steve McCaw

Highlighted Activities

Gulf Oil Spill Response

Immediately following the Deepwater Horizon explosion on April 20, 2010, and the ensuing massive oil spill in the Gulf of Mexico, NTP and NIEHS began coordinated efforts with other Federal agencies (including FDA, OSHA, NHGRI, NIOSH, ATSDR, EPA, National Oceanographic and Atmospheric Administration, U.S. Fish and Wildlife Service, U.S. Geological Survey, and U.S. Coast Guard) to limit the adverse impacts of the oil and dispersants on human health, ecological health, and food sources.

Early efforts by NTP focused upon assembly and distribution of information on characteristics and toxicity of oil and oil dispersants. The NTP is pursuing several lines of research to address concerns regarding the safety of Gulf seafood, hazards to offshore and onshore cleanup workers, and potential long-term health impacts of residual oil in the environment. NIEHS/NTP obtained samples of source oil, tar balls, and the dispersant, COREXIT® EC9500A. The NTP is conducting analytical chemistry studies to better understand the composition of the source oil, tar balls, and oiled sediment collected along the shoreline. The focus of these analyses is on components that are more likely to persist in the environment and potentially lead to residual human exposures. We will use the information from these analytical chemistry efforts to help understand exposures to response workers and to inform exposure assessments in the Gulf Long-term Follow-up Study (GuLF STUDY, see below). The NTP will also

use this information to develop a toxicology research program on polycyclic aromatic hydrocarbons (PAHs). The aim of this program is to further characterize the hazard of PAHs present in oil to determine if routinely monitoring PAHs in environmental media adequately captures the hazard of crude oil exposures, and to better understand whether there are combinations of different PAHs that should be considered in aggregate when establishing safe exposure levels.

The NTP's toxicology assessments will inform the ongoing GuLF Study, which will assess the possible health effects of the oil spill on 55,000 cleanup workers and volunteers in coastal towns across Louisiana, Mississippi, Alabama, and Florida. This longitudinal cohort study, coordinated by NIEHS, is the largest health study of its kind ever conducted, and is an important component of the comprehensive federal response to the oil spill. Information about GuLF STUDY is available at *http://nihgulfstudy.org/*. NIEHS also issued a Request for Applications to fund university and community research in the Gulf on oil spill-related issues such as mental health, respiratory health, and chromosomal damage.

Information about NIEHS oil spill response efforts is available at *http://www.niehs.nih.gov/about/od/programs/gulfspill* and information about the overall federal oil spill response efforts is available at *http://www.restorethegulf.gov/* and *http://cgvi.uscg.mil/media/main.php?g2_itemId=841814&g2_page=6*.

Contact Information: Dr. Scott Masten, *masten@niehs.nih.gov*

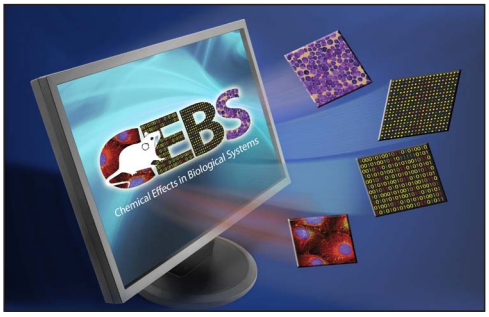
NTP Laboratories Branch

The NTP Laboratories Branch was initiated in FY 2010 to provide high quality laboratory capabilities and support for the performance of agent-specific, targeted research directly related to developing and applying tools of modern toxicology and molecular biology to the evaluation of specific substances of concern to the NTP, issues of central importance to programs of the NTP, or the development of new methods to advance the scientific mission of the NTP. Another focus of the branch is to develop better methods to study the developmental origins of adult diseases. The study design, review, and evaluation processes for the NTP Laboratories will be similar to those for other NTP projects to ensure the highest scientific quality and relevance to the NTP mission.

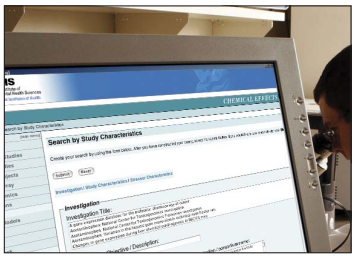
Dr. Michael Waalkes is chief of the Branch and NIEHS scientists Drs. Susanne Fenton, Darlene Dixon, Jean Harry, and Daniel Morgan are all involved in Branch activities, while other NTP scientists are enlisted on an as-needed basis. One of the first studies initiated in the NTP Laboratories is to address data gaps identified in the CERHR soy infant formula evaluation, by conducting a series of lactation-only exposure studies in laboratory animals, with the goal of reducing areas of uncertainty for reaching conclusions on human infants fed soy infant formula.

Contact Information: Dr. Michael Waalkes, *waalkes@niehs.nih.gov*

Chemical Effects in Biological Systems (CEBS): An Integrated Data Management System for the NTP



CEBS is a data management tool that moved to the NTP in 2009. While it was part of the NIEHS Division of Intramural Research, CEBS was designed to house biological data from a variety of studies of different study designs and purposes deposited by NIEHS scientists and members of the public. The unifying theme of CEBS is that the data contained therein are of interest to toxicologists and environmental health scientists. Because CEBS was designed as a public reference repository it can faithfully house "any" type of biological measurements from "any" type of study design. This feature was designed into CEBS to allow data from different sources to be integrated in one place, to permit data mining and analysis. In FY 2010, the NTP was in the process of loading the NTP legacy data into CEBS so that users can mine data from NTP studies as well as from studies submitted from other sources.



CEBS consists of a database, a user interface, and tools for loading data and managing it for display. We have tested the capabilities of CEBS to house NTP data by loading data from legacy genetic toxicology studies, immunotoxicology studies, and current high-throughput assays into the CEBS database. The NTP is modifying the CEBS user interface to permit proper display of the conclusions and raw data from these studies so that users can access them. When this project is completed all the public NTP data will be accessible in CEBS for reference and for data mining.

CEBS captures the details of the study design and execution plus the biological responses of subjects in a way that permits searching, filtering, and sub-setting of the data. The user can view the details of each study, search for particular studies or study subjects of interest based on treatment, response, or other characteristics, and then either analyze the data within CEBS or download for import into other tools. CEBS can be accessed at *http://cebs.niehs.nih.gov*.

Contact Information: Dr. Jennifer Fostel, *fostel@niehs.nih.gov*

Cellular Phone Radiation Emissions

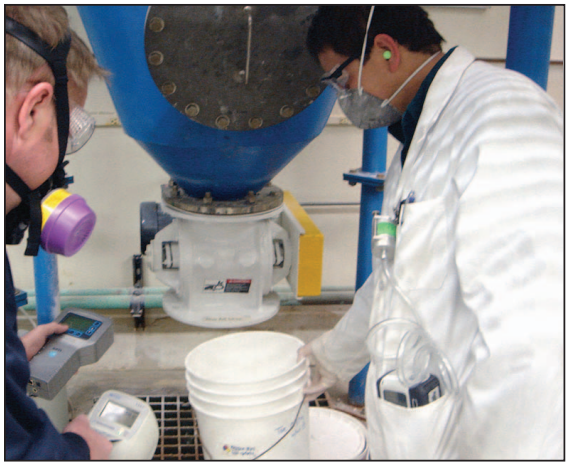
The NTP is conducting a multi-year study to address the potential health-related adverse effects of radiation emitted by cellular phones and cell towers. More than 270 million Americans use wireless communication devices; however, the potential health effects of long-term exposure to radiation emissions from these devices are unknown. The overall goal of the NTP's studies is to determine the potential toxic and/or carcinogenic effects of exposure to cellular phone radiofrequency emissions in laboratory animals. The animal studies are being conducted in three phases: (1) pilot studies to determine appropriate field strengths of emissions, (2) subchronic toxicology using exposures of up to two months, and (3) chronic toxicology and carcinogenicity studies. In FY 2010, NTP was nearing completion of the second phase of the studies and expects to begin the third and final phase in 2011.

These NTP studies will provide information regarding the safety of exposure to radiofrequency radiation and strengthen the science base for determining any potential health effects in humans. These data could contribute to information used by the Federal government, including the FDA, in making decisions about radiofrequency radiation health issues to protect public health and safety.

Contact Information: Dr. Michael Wyde, *wyde@niehs.nih.gov*

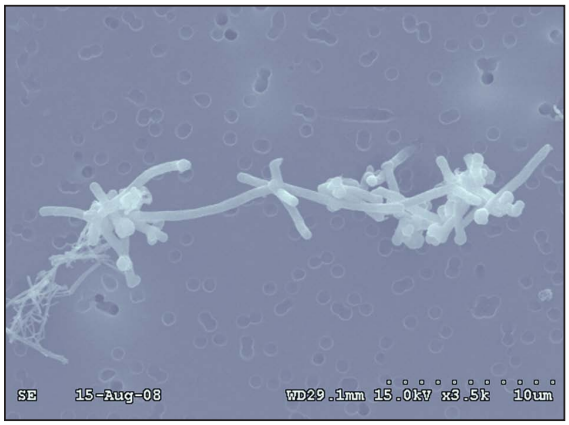
Nanotechnology Safety Initiative

Nanoscale materials are materials that have at least one dimension in the size range of approximately 1-100 nm in size. While they are already appearing in commerce as industrial and consumer products and as novel drug delivery formulations, little research has focused on the potential toxicity of manufactured nanoscale materials. Also, the unique and diverse physicochemical properties of nanoscale materials suggest that their toxicological properties may differ from those of materials of similar composition but larger size.



NIOSH field investigator taking instrument readings during a filter collector drum change by a technician at a nano metal oxide plant.

The NTP is currently engaged in a broad-based research program to address potential human health hazards associated with the manufacture and use of nanoscale materials. This initiative is driven by the current and anticipated future focus on nanotechnology research and development. Ongoing research activities are initially focusing on several classes of materials, including nanoscale metal oxide powders (titanium dioxide and cerium oxide), cadmium-based fluorescent nanocrystalline semiconductors (quantum dots), carbon fullerenes, carbon nanotubes, and metal-based nanoparticles (nanosilver and nanogold).



Scanning electron micrograph of multiwalled carbon nanotubes.

The ultimate goal of this research program is to evaluate the toxicological properties of several nanoscale material classes that represent a cross section of composition, size, surface coatings, and physicochemical properties, and to use these properties to investigate fundamental questions concerning if and how nanoscale materials interact with biological systems and potentially cause adverse effects in humans.

Titanium dioxide

In FY 2010, the NTP was invited to participate in a number of working and advisory groups including the Scientific Oversight Committee for the National Cancer Institute's Nanotechnology Characterization Laboratory and the Interagency Working Group on Nanotechnology Environmental and Health Implications (NEHI) of the Nanoscale Science, Engineering, and Technology Subcommittee of the President's National Science and Technology Council.

Current NTP projects include evaluating the pharmacokinetics of nanoscale silver in rodents. The NTP has completed two subchronic, 90-day inhalation studies of fullerene C60 (exposures to each of two particle sizes, 50 nm and 1 µm, each in both rats and mice via nose-only inhalation). The NTP has completed physicochemical characterization of 24 multi-walled nanotubes of varying sizes, lengths, and vendors. These data are being used to develop subchronic inhalation studies of selected multi-walled nanotubes. Dr. Walker gave six invited presentations on NTP's nanomaterials program in FY 2010.

Contact Information: Dr. Nigel Walker, *walker3@niehs.nih.gov.*

Herbal Medicines and Dietary Supplements

Herbal and dietary supplements are a major focus area for the NTP. The NTP is currently studying many of the 25 top-selling herbal and dietary supplements. Table 5 lists the substances for which studies are completed, ongoing, or planned. The substances can be loosely classified as "women's health" (black cohosh, gum guggul, dong quai), "cancer chemopreventives" (e.g., green tea extract, indole carbinol, resveratrol, melatonin), "anti-aging" (e.g., ginseng, glucosamine/chondroitin sulfate, *Ginkgo biloba*, vincamine), weight loss/sports aids (e.g., *Usnea lichen*/usinic acid, chitosan, *Garcinia cambogia*, bitter orange extract), and "multipurpose" (e.g., *Aloe vera*, *Echinacea*, kava, milk thistle, pulegone/pennyroyal, and senna laxative).

Contact Information: Dr. Nigel Walker, *walker3@niehs.nih.gov.*

Table 5: Herbal Ingredients and Dietary Supplements for Which Studies Are Completed, Ongoing, or Planned

Substance [CASRN]	Project Leader	Use and/or Rationale
Aloe vera (oral) [8001-97-6]	Boudreau	Humans have widespread oral and dermal exposure to *Aloe vera* which lacks adequate toxicity information; there is a suspicion of carcinogenicity. The 1998 FDA Special Nutritional Adverse Event Monitoring System lists *Aloe vera* exposure as associated with numerous adverse effects in humans.
Arbutin [497-76-7]	Chan	Consumer exposure occurs through food, cosmetics, and dietary supplements. There is a lack of adequate toxicological data and suspicion of toxicity based on chemical structure.
Bitter orange extract	Hansen	Consumer exposure is through increasing dietary supplement use (it is the most common replacement for ephedra, banned from use by the FDA in 2003, in dietary supplements for weight loss). There is suspicion of toxicity and a lack of adequate toxicity data.
Butterbur *(Petasites hybridus)* extract [90082-63-6]	Howard	Used as a dietary supplement. There is suspicion of toxicity based on pharmacological activity of constituents and the potential presence of hepatotoxic pyrrolizidine alkaloids.
Chitosan [9012-76-4]	Chhabra	Chitosan is a popular dietary supplement used for weight loss. Several subacute studies in animals show that it has hypercholesterolemic properties and may influence weight gain; it may also cause vitamin and mineral deficiencies. There is a potential for vitamin E depletion and osteoporosis from ingestion.
Chondroitin sulfate/ Glucosamine [9007-28-7]	Leakey	Chondroitin sulfate is a dietary supplement widely used alone and in combination with glucosamine to alleviate pain and inflammation from osteoarthritis. No data are available on the possible adverse or toxic effects from long-term exposure.
Dong quai *(Angelica sinensis root)* and extract	Wyde	Dong quai has widespread use as a dietary supplement and in Chinese herbal medicine as an antispasmodic or blood purifier and for reducing pain, dilating blood vessels, and stimulation, as well as for relaxing uterine muscles. There is suspicion of toxicity based on estrogenic activity and chemical structure, and there is a lack of adequate toxicity data.
Echinacea purpurea, extract [90028-20-9]	Irwin	Echinacea is the most popular herbal supplement in the United States, creating widespread human exposure. It is used to stimulate the immune system, and there is a lack of scientific literature supporting its safety or efficacy.

Substance [CASRN]	Project Leader	Use and/or Rationale
Epigallocatechin (Green tea extract) [989-51-5]	Chan	Epigallocatechin is a potential cancer chemopreventive agent. It is an antioxidant thought to prevent tumorigenesis by protecting cellular components from oxidative damage via free radical scavenging. It is a major component of the polyphenolic fraction of green tea. It requires evaluation regarding its toxicity.
Evening primrose oil *(Oenothera biennis extract)* [90028-66-3]	Germolec	Evening primrose oil is used as a dietary supplement, particularly for autoimmune conditions. There is a lack of adequate toxicological data.
Garcinia cambogia extract [90045-23-1]	Wyde	*Garcinia cambogia* is marketed as an ephedra-free diet aid. There is consumer exposure through increasing dietary supplement use and a lack of adequate toxicity data.
Ginkgo biloba extract [90045-36-3]	Chan	There is potential for widespread exposure through use as a dietary supplement for "improving brain functioning" or "promoting radical scavenging activity." *Ginkgo biloba* clearly demonstrates biological activity and may be consumed in rather large doses for an extended period of time. Some ingredients are known mutagens or suspected carcinogens.
Ginseng [50647-08-0]	Chan	Ginseng has widespread use as a dietary supplement. There is a possibility that ginseng and ginsenosides may have anticarcinogenic activity, and a lack of toxicity information.
Glucosamine [3416-24-8]	Leakey	Glucosamine is a widely used dietary supplement, both alone and in combination with chondroitin sulfate, to alleviate pain and inflammation from osteoarthritis. There are no data on the possible adverse or toxic effects from long-term exposure.
Gum guggul extract	Wyde	Gum guggul has expanding use as a dietary supplement and has demonstrated biological effects on lipid metabolism, thyroid hormone homeostasis, female reproductive tissues, and endogenous nuclear hormone receptors, as well as the potential for serious drug interactions. There is a lack of available information to adequately assess safe use in humans.
Indole-3-carbinol [700-06-1]	Wyde	Indole-3-carbinol is marketed as a dietary supplement with projected rapid growth in sales. It is found in cruciferous vegetables and is under review at NCI as a chemopreventive agent for breast cancer. Substantial evidence exists that indole-3-carbinol can reduce the risk of cancers induced by several carcinogens when administered to animals.
Kava kava extract [9000-3-8]	Chan	Kava kava is a dietary supplement with widespread use. It has also been promoted as a substitute for Ritalin (methylphenidate) in children. Insufficient toxicity data are available. NCI recommended testing kava extract standardized to 30% kavalactones.
Melatonin [73-31-4]	Travlos	Melatonin, a hormone produced by the pineal gland, has become very popular as an over-the-counter hormone supplement as well as being used as a chemotherapeutic agent in cancer. There is a lack of toxicity information and a suggestion that melatonin may have the potential to cause ocular toxicity.
Milk thistle extract [84604-20-6] Silymarin [65666-07-1] Silybin [22888-70-6]	Dunnick	Milk thistle extract is a popular dietary supplement thought to have beneficial effects on the liver; however, there is limited information on its safety. Metabolism studies are needed to resolve questions regarding bioavailability of orally administered milk thistle extract. Milk thistle fruits contain silymarin, the active flavonoid constituent; one of silymarin's principal components is silybin.
Pulegone (Pennyroyal) [89-82-7]	Chan	The nomination of pulegone and menthofuran for testing is based on the potential for human exposure and the absence of carcinogenicity data. Pulegone is a major constituent of pennyroyal, and menthofuran is one of the metabolites of pulegone.
trans-Resveratrol [501-36-0]	Germolec	*trans*-Resveratrol is found in grapes and wine and is currently marketed in pure or extract form as a dietary supplement. It has numerous reported beneficial effects but toxicity is poorly characterized.

Substance [CASRN]	Project Leader	Use and/or Rationale
Retinyl palmitate	Howard	Retinyl palmitate was nominated for phototoxicity and photocarcinogenicity testing based on the increasing widespread use of this compound in cosmetic retail products for sun-exposed skin. There is a need to investigate the biochemical and histological changes in skin caused by retinyl palmitate and the association between topical application of retinoids and enhancement of photocarcinogenesis.
Senna (powdered) [8013-11-4]	Dunnick	The safety of laxatives is currently being reassessed by the FDA as a result of the testing of phenolphthalein for carcinogenicity in rodents. Senna has been reported as positive in the Ames test and a preliminary 2-year rat study showed an increase in lymph node hyperplasia. The FDA Center for Drug Evaluation and Research is requesting a p53 hemizygous study to complement a 2-year rat study sponsored by the manufacturer.
alpha/beta Thujone mixture [546-80-5] [471-15-8]	Hooth	Thujone was identified through a review of direct food additives given "generally recognized as safe" status by the FDA. It has known toxicity that has caused it to be banned from some products. Twenty-four direct food additives in the FDA Priority-Based Assessment of Food Additives contain thujone. There is a potential for widespread consumer and worker exposure.
Usnea barbata, extract [84696-53-7]	Leakey	*Usnea barbata* is used as a dietary supplement for weight loss. Insufficient toxicity data are available.
Usnic acid and *Usnea* herb [125-46-2]	Leakey	Usnic acid and Usnea herb have widespread use in dietary supplements and personal care products. Adequate toxicological data are lacking, and there are numerous human adverse event reports.
Valerian *Valeriana officinalis L.* root extract [8057-49-6] Valerian oil [8008-88-6]	DeVito	toxicological data and concern for adverse developmental and reproductive effects.
Vincamine [1617-90-9]	Chan	Consumer exposure to vincamine occurs through dietary supplement use. There is a suspicion of toxicity and a lack of adequate toxicological data.

[1]Testing Status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* – select "Testing Status of Agents at NTP" and "Study Results and Research Projects."

Use of NTP Products by Other Agencies

Federal and state regulatory agencies use NTP study data and recommendations in considering the need to regulate and test specific chemicals to protect human health. Table 6 lists NTP data and recommendations used in FY 2010.

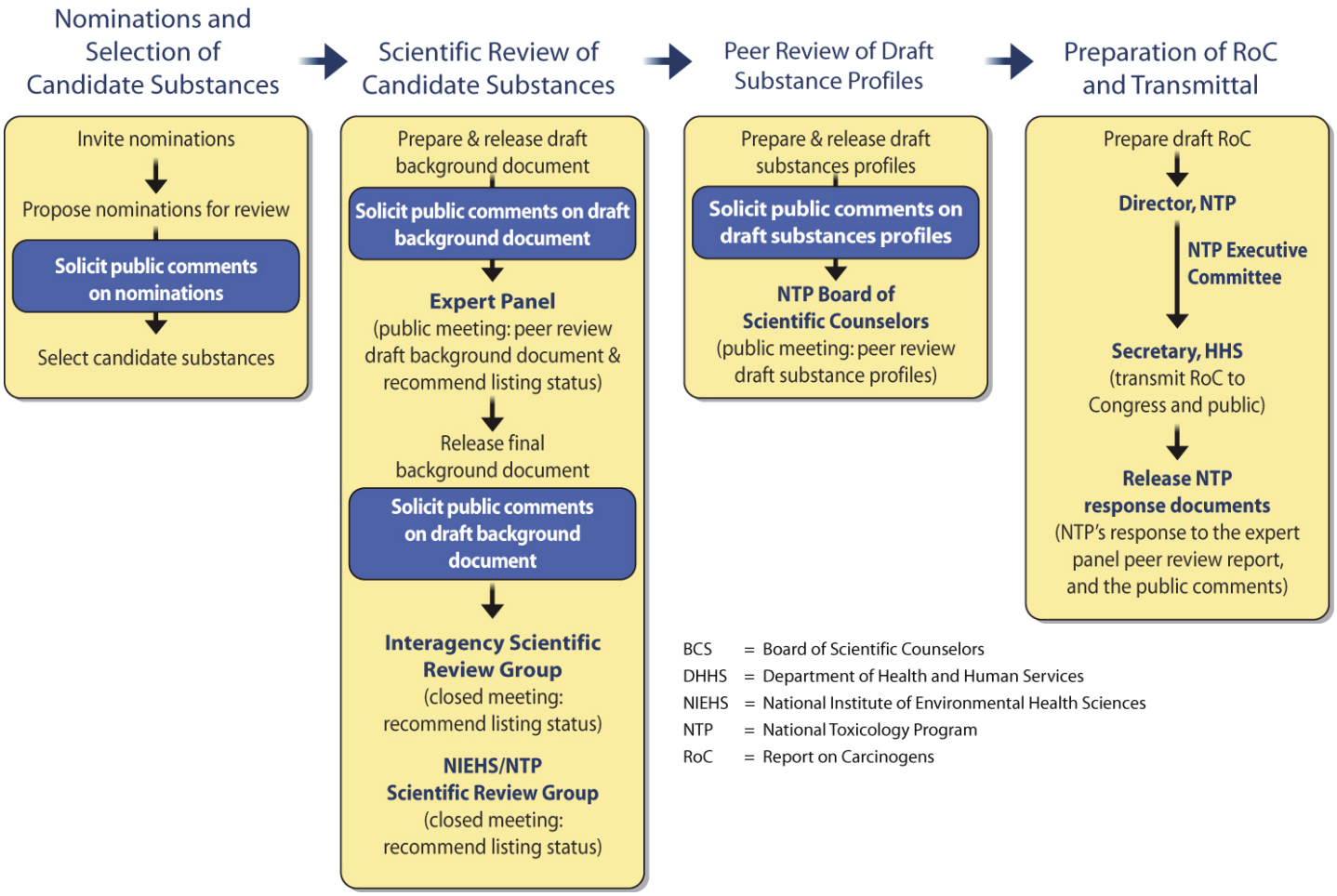
Table 6. Use of NTP Study Data or Recommendations by Federal and State Regulatory Agencies in FY 2010

Agency, Title, Additional Information	NTP Information Cited
California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) ***Announcement of Publication of the Final Public Health Goals for Benzo(A)Pyrene, Methoxychlor, and TCDD (Dioxin) In Drinking Water***	• TR 201 - Bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin [1746-01-6] for possible carcinogenicity (gavage study) • TR 109 - Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Osborne-Mendel rat and B6C3F1 mice (gavage study) • Report of the NTP *ad hoc* panel on chemical carcinogenesis testing and evaluation. Board of Scientific Counselors. 1984. • TR 521 - Toxicology and carcinogenesis studies of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in female Harlan SD rats (gavage study) • Symposium on Significance of Foci of Cellular Alteration in the Rat Liver. *Toxicol Pathol* 17:557-735. 1989.
U. S. EPA ***Community Right-to-Know Toxic Chemical Release Reporting*** EPA is proposing to add 16 chemicals to the list of toxic chemicals subject to reporting under section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) of 1986 and section 6607 of the Pollution Prevention Act of 1990 April 6, 2010 – 75 FR 17333	NTP 11th Report on Carcinogens classified the following as reasonably anticipated to be a human carcinogen: 1-Amino-2,4- Dibromoanthraquinone [81-49-2] 2,2-bis(Bromomethyl)-1,3- propanediol [3296-90-0] Furan [110-00-9] Glycidol [556-52-5] Isoprene [78-79-5] Methyleugenol [93-15-2] 1,6-Dinitropyrene [42397-64-8] 1,8-Dinitropyrene [42397-65-9] 6-Nitrochrysene [7496-02-8] 4-Nitropyrene [57835-92-4] o-Nitroanisole [91-23-6] Nitromethane [75-52-5] Phenolphthalein [77-09-8] Tetrafluoroethylene [116-14-3] Tetranitromethane [509-14-8] Vinyl Fluoride [75-02-5]

Report on Carcinogens

The Report on Carcinogens (RoC) is a congressionally mandated listing [Section 301(b)(4) of the Public Health Services Act, 42 U.S.C. 241(b)(4)] of substances (1) that either are *known to be human carcinogens* or *may reasonably be anticipated to be human carcinogens* and (2) to which a significant number of persons residing in the United States are exposed. Each substance listed in the RoC has a profile, which contains the listing status, a summary of the cancer studies supporting the listing status, information on human exposure, and Federal regulations to reduce exposure. The RoC is a cumulative report and consists of substances newly reviewed in addition to those listed in previous editions. The Secretary of Health and Human Services has delegated preparation of the RoC to the NTP, with assistance from other Federal health and regulatory agencies. Dr. Ruth Lunn is the Director of the RoC Center. SRA International, Inc., provided contract support for preparation of the RoC in FY 2010.

Figure 3: NTP Report on Carcinogens Review Process



BCS = Board of Scientific Counselors
DHHS = Department of Health and Human Services
NIEHS = National Institute of Environmental Health Sciences
NTP = National Toxicology Program
RoC = Report on Carcinogens

Reviewing nominations to the RoC is a multi-step, formal, and open process, as shown in Figure 3 and on the RoC website (*http://ntp.niehs.nih.gov/go/15208*). The nomination of substances for listing in or removal from the RoC is open to all interested individuals and groups. The RoC Center prepares a draft background document on each substance under review that is peer-reviewed by an external scientific ad hoc panel at a public meeting. Three independent scientific groups make recommendations to the NTP on the listing status of candidate substances using established listing criteria. Taking into account recommendations from the three review groups and the public comments, the NTP drafts a substance profile, which contains its preliminary listing status recommendation, the science that supports the recommendation, and information on use, production, exposure, and current regulations. The NTP BSC meets publicly to peer review the draft substance profile. Public comments are solicited several times during the review process and are provided to each review group as available. The NTP prepares the draft RoC (which contains substance profiles for newly proposed and listed substances and substances listed in previous editions of the RoC) for review and comment by the NTP Executive Committee. The NTP Director receives the input from all reviews plus the public comments and submits the final draft RoC to the Secretary, DHHS, for review and approval.

Candidate substances for the 12th RoC are listed in Table 7. Scientific review of candidate substances for the 12th edition of the RoC, which was carried out using a formal process (see Figure 3), was completed in FY 2010 with the review of formaldehyde. Formaldehyde is currently listed in the 11th RoC as reasonably anticipated to be a human carcinogen; it was reviewed for the 12th RoC for a possible change in listing status. The RoC Center convened an expert panel to peer review the draft background document for formaldehyde on November 2-4, 2009, in Research Triangle Park, NC. The expert panel recommended listing formaldehyde as a known human carcinogen based on sufficient evidence of carcinogenicity from studies in humans and supporting studies on mechanisms of carcinogenesis.

The NTP BSC peer reviewed the draft substance profiles for cobalt-tungsten carbide: hard metals and powders, glass wool fibers, and formaldehyde at the June 21-22, 2010 meeting.

Table 7: Candidate Substances for the 12th Report on Carcinogens in FY2010

Candidate Substance [CASRN] Nominator	Primary Uses/Exposures	Basis of Nomination
Aristolochic Acids NIEHS	A family of nitrophenanthrene carboxylic acids that occurs naturally in plants in the *Aristolochiaceae* family, primarily of the genera *Aristolochia* and *Asarum*. Botanical products from plants containing aristolochic acids are used in traditional folk medicines, particularly in Chinese herbal medicine, and have been used inadvertently as part of a weight-loss regimen.	IARC finding of sufficient evidence of carcinogenicity in animals and limited evidence in humans. (IARC Monograph Vol. 82, 2002).
Captafol [2425-06-01] NIEHS	A broad-spectrum fungicide that has been widely used since 1961 for the control of fungal diseases in fruits, vegetables, and some other plants. Use of captafol in the United States was banned in 1999.	IARC finding of sufficient evidence of carcinogenicity in animals (IARC Monograph Vol. 53, 1991). IARC also noted that captafol gives positive results in many genetic assays, including the *in vivo* assay for dominant lethal mutation.
Cobalt–Tungsten Carbide: Powders Hard Metals NIEHS	Composites of tungsten-carbides with a metallic cobalt, used to make cutting and grinding tools, dies, and wear products for a broad spectrum of industries, including mining and oil and gas drilling.	Recent human cancer studies on the hard metal manufacturing industry showing an association between exposure to hard metals (cobalt tungsten-carbide) and lung cancer.
Formaldehyde [50-00-0] NIEHS – for reclassification	Primarily used to produce resins for the production of many different products, including plastics, adhesives and binders for wood products, pulp and paper, and synthetic fibers, and in textile It is also used as a disinfectant and preservative and as an intermediate for many industrial chemicals.	Nominated for reconsideration based on the 2004 IARC review, which concluded that there was sufficient evidence for the carcinogenicity of formaldehyde in humans (IARC Monograph finishing. Vol. 88, 2004).

Candidate Substance [CASRN] Nominator	Primary Uses/Exposures	Basis of Nomination
Glass Wool Fibers North American Insulation Manufacturers Association nominated glass wool (respirable size) for delisting	Glass wool fibers, which are a type of synthetic vitreous fibers, are an inorganic fibrous material manufactured primarily from glass and processed inorganic oxides. The major uses of glass wool are in thermal, electrical, and acoustical insulation, weatherproofing, and filtration media. Some special-purpose glass wool fibers are used for high-efficiency air filtration media and acid battery separators.	Insulation glass wool: IARC finding of limited evidence of carcinogenicity in animals and evaluation as not classifiable as to its carcinogenicity to humans (Group 3; IARC Monograph Vol. 81, 2002). Special-purpose glass fibers: IARC finding of sufficient evidence of carcinogenicity in animals (IARC Monograph Vol. 81, 2002).
ortho-Nitrotoluene [88-72-2] NIEHS	A chemical intermediate used in the synthesis of azo dyes. It is also used (either directly or as an intermediate) in the production of other dyes, agricultural chemicals, rubber chemicals, pesticides, petrochemicals, pharmaceuticals, and explosives.	Results of an NTP bioassay (NTP Technical Report 504, 2002), which reported *clear evidence of carcinogenic activity* in rats and mice.
Riddelliine [2346-96-0] NIEHS	Found in a class of plants growing in the western United States. Cattle, horses, and sheep ingest these toxic plants.	Results of an NTP bioassay (NTP Technical Report 508, 2003), which reported *clear evidence of carcinogenic activity* in male and female rats and mice.
Styrene [100-42-5] Private Individual	Used worldwide in the production of polymers, which are incorporated into products such as rubber, plastic, insulation, fiberglass, pipes, automobile parts, food containers, and carpet backing.	IARC finding of limited evidence of carcinogenicity in animals and limited evidence of carcinogenicity in humans (IARC Monograph Vol. 82, 2002).

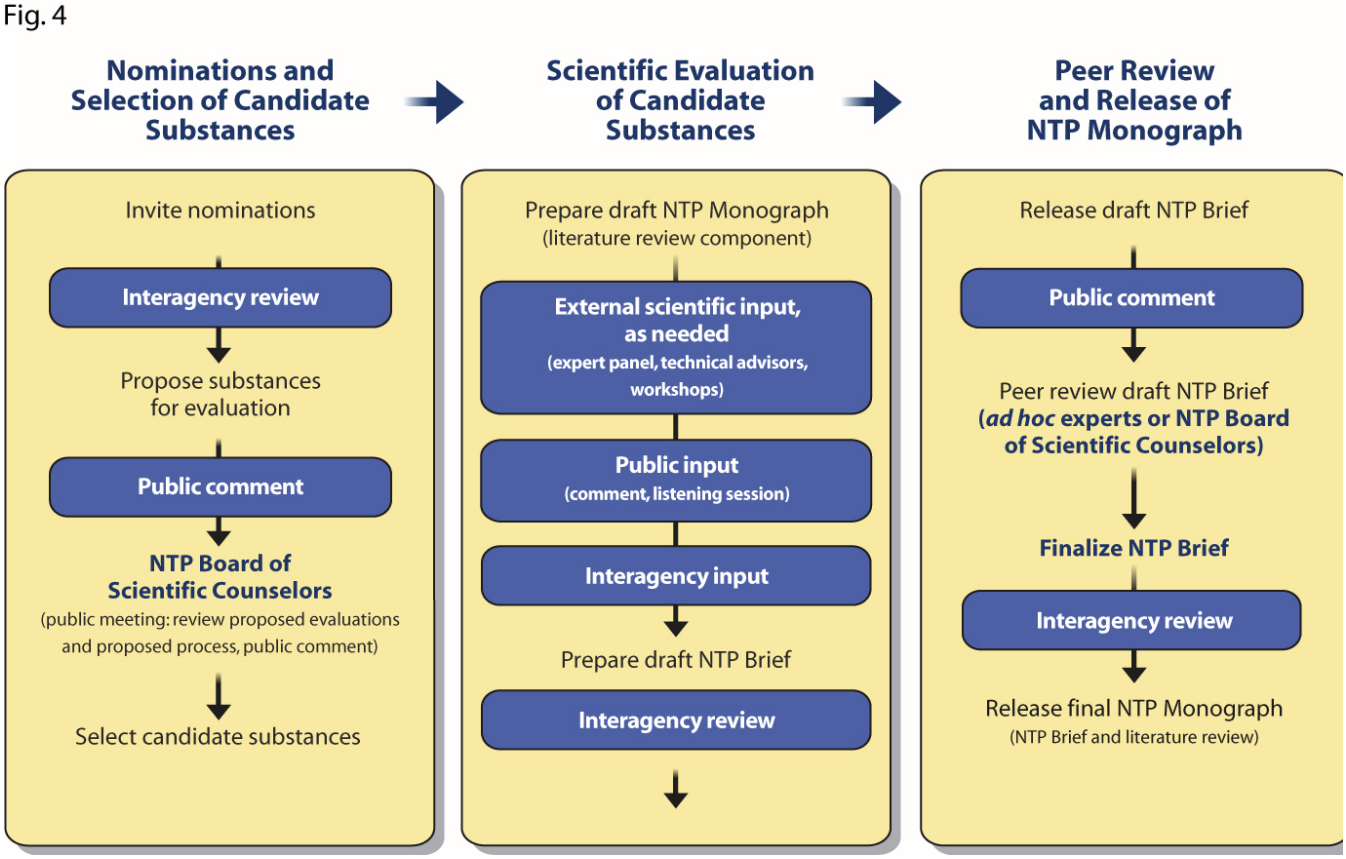
International Agency for Research on Cancer (IARC). IARC Monographs are available from *http://monographs.iarc.fr/*.
NTP Technical Reports are available at *http://ntp.niehs.nih.gov/* see "NTP Study Reports."

Contact Information: Report on Carcinogen Center, Dr. Ruth Lunn, *lunn@niehs.nih.gov*.
RoC website: *http://ntp.niehs.nih.gov* select "Report on Carcinogens."

Center For the Evaluation of Risks to Human Reproduction

The Center for the Evaluation of Risks to Human Reproduction (CERHR) was established in 1998 to serve as an environmental health resource to the public and regulatory and health agencies. CERHR publishes monographs that assess the potential for substances to cause adverse effects on reproduction and development in humans. CERHR selects substances for evaluation based on several factors, including production volume, extent of human exposures, public concern about the chemical hazard, and the extent of published data from studies of reproductive or developmental toxicity. Dr. Kristina Thayer is the Director of CERHR.

Fig. 4



Revision of the CERHR Evaluation Process

The NTP revised the CERHR evaluation process (Figure 4) for preparation of NTP monographs on environmental substances to (1) enhance scientific development of CERHR products and to maximize efficiency and utilization of resources and (2) broaden the scope of analysis topics beyond those traditionally associated strictly with reproduction and development. The process was changed to allow flexibility to better tailor an evaluation to meet programmatic needs depending upon the topic, scope, nature and extent of the literature, scientific complexity, and time considerations. The new process retains elements of the past, including opportunity for external scientific input, public input at multiple points, interagency input, and external peer review, and addresses the weakness of limited flexibility. NTP presented this change in process to the BSC in December 2009 (*http://ntp.niehs.nih.gov/go/9741*). Overall, the BSC supported the change in the evaluation process to allow flexibility in the approach used to gain input.

Evaluation of Soy Infant Formula

CERHR convened a public, expert panel meeting on December 16-18, 2009, in Alexandria, Virginia to evaluate soy infant formula. Soy formula is an infant food made using soy protein and other components. It is fed to infants as a supplement or replacement for human milk or cow milk formula. Soy formula contains isoflavones, naturally occurring compounds found primarily in beans and other legumes including soybeans, peanuts, and chickpeas.

The 14-member *ad hoc* scientific panel reviewed and evaluated the available scientific data on soy infant formula. In their deliberations, the expert panel considered the quality and strength of the scientific evidence that soy formula or its isoflavone constituents might cause adverse effects on human development. The expert panel also identified gaps in the available scientific data on the possible effects of soy formula and suggested areas where additional research is needed. The expert panel expressed minimal concern for adverse developmental effects in infants fed soy infant formula.

Based upon information in the expert panel report, public comments, and other literature since the expert panel met, the NTP prepared its NTP Brief with its preliminary conclusion regarding soy formula and potential effects on human reproduction and development. The BSC peer reviewed the draft NTP Brief at its meeting on May 10, 2010. The BSC supported the NTP's conclusion of *minimal* concern for adverse effects on development in infants who consume soy infant formula. This level of concern represents a "2" on the five-level scale of concern used by the NTP that ranges from *negligible* concern ("1") to *serious* concern ("5"). The NTP released the final NTP Brief on Soy Infant Formula on September 16, 2010 (*http://cerhr.niehs.nih.gov/evals/genistein-soy/soyformula/soyformula.html*).

The NTP BSC further supported a research program proposed by CERHR to address some key data gaps identified in the soy infant formula evaluation. CERHR initiated this research program, which includes a series of lactation-only exposure studies with the goal of reducing areas of uncertainty for reaching conclusions on human infants fed soy infant formula from the laboratory animal data. These studies will be carried out in the new NTP Laboratory Branch (see page 31).

Evaluation of Low-Level Lead

CERHR began an evaluation of the adverse effects of low-level lead exposure, which will focus on epidemiological data on blood lead levels <10 µg/dL, because the health effects at higher blood lead levels are well established. The current occupational exposure limit is 40 µg/dL in workers (including women of childbearing age), although epidemiological data show adverse effects on reproduction and development at lower blood lead levels. The scope of the evaluation will include epidemiological findings on health effects other than reproduction and development (e.g., cardiovascular effects in adults) in order to maximize the utility of the evaluation. The evaluation is designed to address (1) the weight of the evidence for adverse health effects associated with blood lead levels of <10 µg/dL, (2) the health effect(s) associated with blood lead levels <10 µg/dL, (3) the life stages (prenatal, childhood, adolescence, or adulthood) in which lead's effects are identified, (4) the blood lead level associated with the health effect(s), and (5) additional biomarkers of exposure associated with the effect (e.g., bone lead) and the relationship of this biomarker to the blood lead level. The NTP BSC reviewed the proposed approach for the evaluation at the May 10, 2010 meeting and gave its support. Information is available at *http://cerhr.niehs.nih.gov/evals/Lead/lead.html*.

Evaluation of the Role of Environmental Chemicals in the Development of Diabetes and Obesity

CERHR presented a concept proposal at the December 9-10, 2010 BSC meeting for a State of the Science Workshop on environmental exposures and diabetes/obesity. The justification for this assessment is that diabetes and obesity are major threats to human health. Forty percent of people over the age of 20 have diabetes or pre-diabetes and ~70% of type 2 diabetes risk can be attributed to overweight/obesity. Diabetes and obesity are often discussed in the context of developmental origins of adult disease or prenatal programming. There is growing scientific and public interest in this issue. The goals and expected outcomes of the assessment are to (1) complete a critical assessment of the current literature and (2) focus future research directions. CERHR scheduled the workshop for January 2011 (see *http://cerhr.niehs.nih.gov/evals/diabetesobesity/index.html*).

Evaluation of Cancer Chemotherapy during Pregnancy

CERHR is evaluating the evidence for developmental effects of exposure to cancer chemotherapy *in utero*, with the main focus on clinical data in humans, to be supplemented with biomedical and toxicological literature in animals. The goal of the monograph is to provide clinicians, patients, and researchers with a comprehensive review of the incidence and types of adverse effects seen in humans exposed *in utero* to cancer chemotherapeutic agents. The key objectives of the document are to (1) identify the complete published scientific literature on chemotherapy during pregnancy in humans, focusing on the most common cancers occurring during pregnancy; (2) critically evaluate the strength and consistency of the literature on embryo, fetal, and postnatal outcomes in humans by cancer type, chemotherapeutic agent, and trimester of exposure; (3) develop weight of evidence conclusions on the occurrence of adverse effects at different gestational stages, by agent; and (4) identify data gaps and research needs for evaluating the effects of exposure to cancer chemotheraputics *in utero*. The NTP BSC reviewed the proposal at the June 21-22, 2010 meeting and supported NTP moving forward (*http://cerhr.niehs.nih.gov/evals/pregnancychemo/index.html*).

CERHR staff recognition

Dr. Michael Shelby, former CERHR Director, was recognized by his peers at the Environmental Mutagen Society meeting in October 24-28, 2009 for his 30 years of contribution to Mutation Research as an author, reviewer, and editor, and for his long career in mutagenesis research.

Contact Information: NTP Center for the Evaluation of Risks to Human Reproduction, Dr. Kristina Thayer, Director, *thayer@niehs.nih.gov*.
CERHR website: *http://cerhr.niehs.nih.gov*

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

The development, validation, acceptance and harmonization of new, revised, and alternative toxicological test methods are coordinated in the Federal government through ICCVAM. NIEHS established ICCVAM in 1997 to implement a directive in the 1993 NIH Revitalization Act to develop a process to achieve the regulatory acceptance of scientifically valid alternative testing methods. Alternative methods are those methods that reduce, refine, or replace the use of animals. NICEATM was established in 1998 to administer ICCVAM, provide scientific support for ICCVAM activities, and conduct independent validation studies on promising test methods. The ICCVAM Authorization Act of 200 (42 U.S.C. 285l-3) established ICCVAM as a permanent interagency committee under NICEATM, and specified the purposes and duties of the committee. Dr. William Stokes (Rear Admiral, U.S. Public Health Service) is the NICEATM Director and Executive Director of ICCVAM. Integrated Laboratory Systems, Inc., provided contract support for NICEATM in FY 2010.

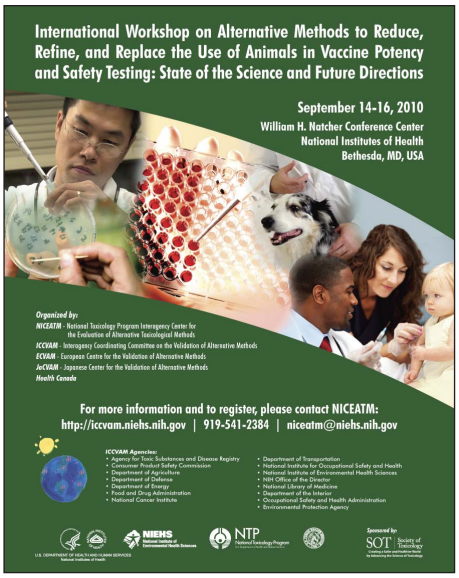
ICCVAM and NICEATM work to promote the validation and regulatory acceptance of new, revised, and alternative toxicological test methods that are more predictive of human and ecological effects than those currently available and that refine, reduce, and replace animal use whenever possible. The desired outcomes from these new methods are to improve agencies' abilities to assess risk and make regulatory decisions, promote more humane animal use, and reduce and replace animal use. NICEATM, in conjunction with ICCVAM, convenes scientific peer review panels to evaluate the validation status of proposed alternative testing methods for which validation studies have been completed to assess their accuracy and reproducibility across multiple labs. ICCVAM then develops formal test method recommendations for acceptance consideration by agencies, and proposes recommended test methods for adoption by international organizations. NICEATM and ICCVAM also convene workshops and expert panels to evaluate the adequacy of existing methods, identify promising test methods for further development and validation, evaluate the interim validation status of methods, and evaluate proposed validation studies.

NICEATM receives test method nominations and submissions for ICCVAM to consider and review (see *http://iccvam.niehs.nih.gov*). Test methods can be nominated for validation studies or technical reviews. The ICCVAM evaluation process involves an initial assessment by NICEATM of the adequacy and completeness of the test method nomination or submission, and a determination by ICCVAM of the priority of the proposed method for technical evaluation or validation studies. Once a proposed test method is accepted for evaluation or validation, ICCVAM assembles an interagency working group with appropriate scientific and regulatory expertise to collaborate with NICEATM on the evaluation process. Depending on the validation status of the proposed test method, ICCVAM, in conjunction with NICEATM, develops recommendations and priorities for appropriate evaluation activities. Such efforts might include an expert workshop, an expert panel meeting, a peer review meeting, an expedited peer review process, or a validation study. Information on the status and results of NICEATM and ICCVAM activities, including meeting reports and background documents, is available on the NICEATM-ICCVAM website. ICCVAM has contributed to the approval or endorsement of 33 alternative safety-testing methods by Federal regulatory agencies since its establishment in 1997. Recent NICEATM publications, meetings, and test methods currently under review, and project status are presented in Tables 8, 9, 10, and 11 respectively.

On June 11, 2010, NICEATM published the ICCVAM Biennial Progress Report, which detailed ICCVAM activities and progress from 2008-2009. Among the highlights included in the report are ICCVAM's recommendations of two *in vitro* ocular safety test methods, two *in vitro* assays to assess the potential of chemicals and products to cause acute oral poisoning, and an updated test method protocol and procedures for the murine local lymph node assay. A pdf version of the report can be accessed on line at *http://iccvam.niehs.nih.gov/about/ICCVAMrpts.htm*.

Dr. Stokes delivered the keynote address at an event held to recognize the establishment of KoCVAM, the inaugural KoCVAM International Symposium, which was held at Seoul National University in South Korea on November 3, 2009. In his talk, "Validation and Regulatory Acceptance of Alternative Methods for Safety Testing: Recent Progress and Future Directions," he stressed the importance of high quality validation studies to enable regulatory acceptance and use of new safety test methods. He also visited the Korean FDA and the National Institute of Food and Drug Safety, the parent agency of KoCVAM.

Dr. Stokes delivered the plenary lecture at the 22nd Annual Meeting of the Japanese Society for Alternatives to Animal Experiments (JSAAE), held November 13-15, 2009, at Osaka University. While in Japan, he also participated in an international workshop on dermal safety of cosmetics and chemicals and attended an advisory committee meeting of the Japanese Center for the Validation of Alternative Methods (JaCVAM). He also met with the JaCVAM director and staff members to discuss joint validation and evaluation activities with NICEATM and ICCVAM.



Alternative methods of vaccine safety testing were the focus of an international workshop held September 14-16, 2010, at NIH in Bethesda, MD. The workshop, which was organized by NICEATM and ICCVAM in partnership with ECVAM, JaCVAM, and Health Canada, hosted nearly 200 scientists from 13 countries. Participants at the International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions worked to advance the availability of alternative methods for vaccine potency and safety testing while ensuring continued protection of human and animal health. NICEATM and ICCVAM have included vaccine testing as one of four high priority areas in their *2008-2012 Five-Year Plan*.

In FY 2011, NICEATM-ICCVAM is planning to convene the Independent Peer Review Panel Meeting: Evaluation of an *In Vitro* Stably-Transfected Estrogen Receptor Transcriptional Activation Assay for Identification of Potential Endocrine Disruptor Activity, scheduled for March 29-30, 2011, at NIH in Bethesda, MD. NICEATM-ICCVAM will also be holding a series of workshops in FY 2011, Best Practices for Regulatory Safety Testing.

Table 8: NICEATM-ICCVAM Publications in FY 2010

Date	Title
Mar 23, 2010	NICEATM-ICCVAM Brochure (revised March 2010)
Jun 10, 2010	ICCVAM 2008-2009 Biennial Report
Jun 29, 2010	ICCVAM Test Method Evaluation Report on the Murine Local Lymph Node Assay: DA A Nonradioactive Alternative Test Method to Assess the Allergic Contact Dermatitis Potential of Chemicals and Products
Jun 29, 2010	ICCVAM Test Method Evaluation Report on the Murine Local Lymph Node Assay: BrdU-ELISA A Nonradioactive Alternative Test Method to Assess the Allergic Contact Dermatitis Potential of Chemicals and Products
Sep 13, 2010	ICCVAM Test Method Evaluation Report: Recommendations for Routine Use of Topical Anesthetics, Systemic Analgesics, and Humane Endpoints to Avoid or Minimize Pain and Distress in Ocular Safety Testing
Sep 13, 2010	ICCVAM Test Method Evaluation Report on a Proposed *In Vitro* Testing Strategy for U.S. Environmental Protection Agency Ocular Hazard Classification and Labeling of Antimicrobial Cleaning Products
Sep 13, 2010	ICCVAM Test Method Evaluation Report: Current Validation Status of *In Vitro* Test Methods Proposed for Identifying Eye Injury Hazard Potential of Chemicals and Products
Sep 13, 2010	ICCVAM Test Method Evaluation Report: Recommendation to Discontinue Use of the Low Volume Eye Test for Ocular Safety Testing

Table 9: NICEATM-ICCVAM Workshops and Peer Review Meetings in FY 2010

Date	Meeting	Topics
Jun 17-18, 2010	Scientific Advisory Committee on Alternative Toxicological Methods (U.S. EPA, Research Triangle Park, NC)	• Regulatory acceptance and availability of ICCVAM-recommended alternative test methods • Assessment of acute and chronic pain in animals • Federal agency research, development, translation and validation activities relevant to the NICEATM-ICCVAM Five-Year Plan • Current issues in the validation of alternative methods for assessing chemically-induced eye injuries • Updates on international collaborations • Alternative methods of vaccine potency testing
Sep 14-16, 2010	International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions (Natcher Conference Center, NIH, Bethesda, MD)	• Review of the state of the science of alternative methods in vaccine potency and safety testing, and discussion of ways to promote their implementation • Identification of knowledge and data gaps that must be addressed to develop alternative methods to further reduce, refine, and replace the use of animals in vaccine potency and safety testing • Identification and prioritization of research, development, and validation efforts needed to address these knowledge and data gaps in order to advance alternative methods for vaccine potency and safety testing, while ensuring continued protection of human and animal health

Table10: Actions on Nominations or Submissions by NICEATM-ICCVAM in FY 2010

Test Method Nomination or Submission	Nominator or Sponsor/Activity Status
Request for assessment of the validation of the LLNA for classification of sensitizers	U. S.CPSC/ICCVAM has recommended that the LLNA may be used to test any chemical or product for allergic contact dermatitis hazard potential unless the chemical or product to be tested has properties that may interfere with the ability of the LLNA to detect sensitizing substances.
MCF-7 Estrogenic Activity Cell Proliferation Assay	CertiChem, Inc./Validation study ongoing, completion expected Spring 2011.
BG1Luc ER TA test method (also known as the LUMI-CELL® test method)	Xenobiotic Detection Systems, Inc./Validation study complete. NICEATM staff and international collaborators presented an update on the international validation study of the BG1Luc ER TA test method at the 2010 meeting of the Society of Toxicology. Expert panel to review background draft review document, March 2011.
In vitro test method for assessment of the eye irritation potential of antimicrobial cleaning products (ACMPs)	Alternative Testing Steering Committee: S.C. Johnson and Son, Inc., The Procter and Gamble Company, and The Accord Group/ ICCVAM concluded that there are currently insufficient data with which to adequately demonstrate that the proposed strategy can classify test substances to all four EPA ocular hazard categories. ICCVAM also concluded that the data were insufficient to support definitive recommendations on an alternate AMCP testing strategy to classify substances in all four EPA ocular hazard categories. ICCVAM recommended future studies that could further characterize the usefulness and limitations of a testing strategy for AMCPs. These recommendations were transmitted to U.S. Federal agencies, September 2010.

Table 11: NICEATM-ICCVAM Recommendations in FY 2010	
Test Method	**ICCVAM Recommendations/Agency Status**
Routine Use of Topical Anesthetics, Systemic Analgesics, and Humane Endpoints in Ocular Safety Testing	Recommended to U.S. Federal agencies, September 2010
Cytosensor microphysiometer (CM) ocular test method	Recommended to U.S. Federal agencies, September 2010
Proposed *in vitro* testing strategy that uses three *in vitro* test methods to assess the eye irritation potential of antimicrobial cleaning products	Further studies recommended, September 2010
OECD Test Guideline (TG) 487, *In Vitro* Micronucleus Assay	November 2009: ICCVAM and its Genetic Toxicity Working Group (GTWG) recommended approval of TG 487 based on the results of the cytotoxicity study data provided by European Union and U.S. laboratories from November 2008 to July 2009
Expanded applicability domain for the LLNA	ICCVAM recommended to U.S. Federal agencies in 2010
LLNA performance standards; updated LLNA test method protocol (20% animal reduction)	U.S. acceptance in 2010 OECD adoption (TG 429), July 2010
Reduced LLNA method (40% animal reduction)	U.S. acceptance in 2010 OECD adoption (TG 429), July 2010
Nonradioactive LLNA versions (BrdU-ELISA and DA)	ICCVAM recommended to U.S. Federal agencies, June 2010 OECD adopted test guidelines (TG 442A, TG 442B), July 2010

Contact information: NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, Dr. William Stokes, Director. *niceatm@niehs.nih.gov* or NICEATM/ICCVAM website *http://iccvam.niehs.nih.gov*

Nomination, Selection, Evaluation, and Review

Nominations for Study

The NTP maintains a balanced research and testing program that provides data addressing a wide variety of issues important to public health. The NTP actively seeks to identify and select for study chemicals and other substances for which sufficient information is not available to adequately evaluate potential human health hazards. The NTP accomplishes this goal through a formal open nomination and selection process. Substances considered appropriate for study generally fall into two broad, yet overlapping, categories:

1. Substances judged to have high concern as a possible public health hazard based on the extent of human exposure and/or suspicion of toxicity.
2. Substances for which toxicological data gaps exist and additional studies would help assess potential human health risks, e.g., by extrapolating data across species or by evaluating dose-response relationships.

Input is also solicited regarding the nomination of studies that test hypotheses to enhance the predictive ability of future NTP studies, address mechanisms of toxicity, or fill significant gaps in the knowledge of the toxicity of classes of chemical, biological, or physical substances. Increased efforts continue to focus on:

- Improving the quality of the nominations of chemicals, environmental agents, or issues for study so that public health and regulatory needs are addressed.
- Broadening the base and diversity of nominating organizations and individuals.
- Increasing nominations for studying non-cancer toxicological end points.

The nomination process is open to the public. The NTP routinely solicits nominations at conferences and workshops; through the NTP newsletter, *Federal Register* notices, the NTP website (*http://ntp.niehs.nih.gov*), and from interested individuals and groups. Also, NCI, FDA, NIOSH, and NIEHS routinely identify and forward nominations to the NTP. The NTP also reviews environmental occurrence and human exposure databases and the scientific literature to identify substances of potential interest.

Contact Information: Office of Nomination and Selection, Dr. Scott Masten, *masten@niehs.nih.gov.*
Nomination website: *http://ntp.niehs.nih.gov/* select "Nominations to the Testing Program."

Review and Selection Process

Reviewing and selecting substances and issues nominated for study is a multi-step process (see figure 5 and *http://ntp.niehs.nih.gov/go/156*) that addresses a broad range of concerns from participating representatives from the NIEHS, other Federal agencies, the NTP Board of Scientific Counselors (see page 8), the NTP Executive Committee (see page 13), and the public. This multi-step evaluative process provides the NTP with direction and guidance to ensure that its testing program addresses toxicological concerns in all areas of public health and that there is balance among the types of substances selected for study (e.g., industrial chemicals, consumer products, therapeutic agents). Figure 5 summarizes the study nomination review process, and Table 12 lists the nominations reviewed in FY 2010.

NTP Study Nomination Review Process

Fig. 5

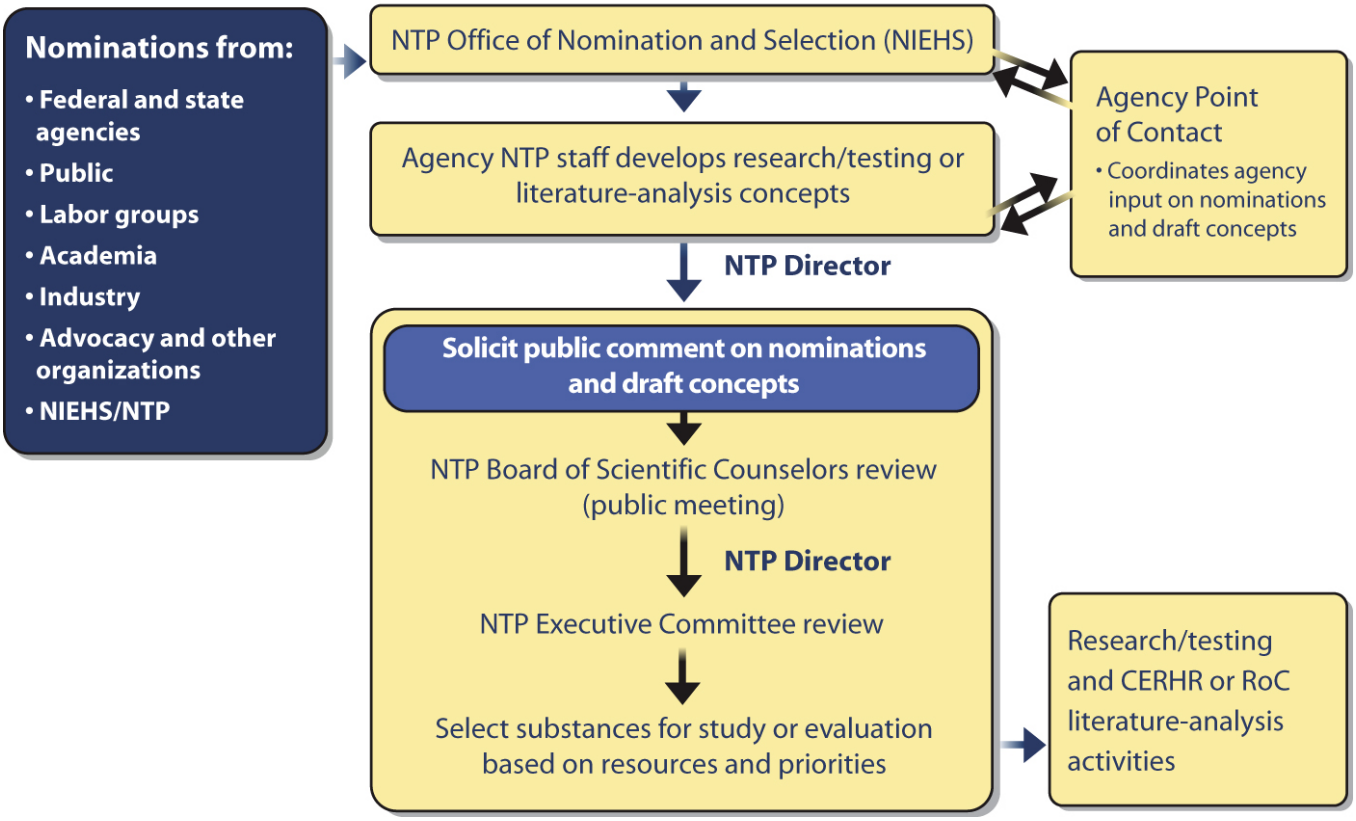


Table 12: Nominations Reviewed in FY 2010

Substance [CASRN]	Nominator	Nomination Rationale	Study Recommendation
Butterbur *(Petasites hybridus)* extract [90082-63-6]	NIEHS	• Use as a dietary supplement • Lack of toxicological data • Suspicion of toxicity based on pharmacological activity of constituents • Potential presence of hepatotoxic pyrrolizidine alkaloids	• Chemical characterization and *in vitro* toxicity screening assays for multiple butterbur preparations • Subchronic toxicity studies • Multigeneration developmental and reproductive toxicity studies • Chronic toxicity and carcinogenicity studies
Evening primrose oil (*Oenothera biennis* extract) [90028-66-3]	NIEHS	• Use as a dietary supplement, particularly for autoimmune conditions • Lack of adequate toxicological data	• Subchronic toxicity studies • Immunotoxicity studies • Multigeneration reproductive toxicity studies
Hydroquinone [123-31-9]	FDA	• Use in drugs and cosmetics • Evidence of carcinogenicity from oral exposures in prior NTP studies • Insufficient toxicological data for regulatory hazard determination	• Comparative metabolism and disposition studies in mice and rats by oral and dermal routes of administration • Subchronic toxicity studies and carcinogenicity studies (dermal route of administration) • Multigeneration reproductive toxicity studies (oral route of administration)

Substance [CASRN]	Nominator	Nomination Rationale	Study Recommendation
Hydroxyurea [127-07-1]	NIEHS Private Individual	• Long-term safety concern when used as therapy for sickle cell anemia; • Critical data need, identified by CERHR, for multi-generation experimental animal studies to assess the long-term effects of prenatal and postnatal exposures on postnatal development including developmental neurotoxicity, reproductive function, and carcinogenicity	• Multigenerational developmental and reproductive toxicity studies including neurotoxicity and immunotoxicity assessments • Carcinogenicity studies
Silica flour [14808-60-7]	Private Individual	• Use in skin care and pharmaceutical products • Inhalation exposures associated with autoimmune disease • Lack of toxicity data for oral and dermal exposures • Insufficient data to evaluate dose-response for renal and autoimmune effects by any route of exposure	• Chemical characterization of silica flour-containing products • Absorption and tissue disposition following oral administration • Immunotoxicity studies (oral route of exposure)
Isoflavones in soy infant formula	NIEHS	• Widespread exposure • Concern for potential adverse effects on human development; • Address certain critical data gaps and research needs identified in the NTP CERHR Expert Panel Report on Soy Infant Formula	• Studies to determine the feasibility soy of direct oral administration of infant formula to rodents (rats and/or mice) during the period of lactation • Reproductive development and fertility study in rodents with soy infant formula and a mixture of isoflavones at the ratio found in soy infant formula (oral administration to pups during period of lactation) • Uterotrophic assay to assess interactions among the individual isoflavones in soy infant formula • Pharmacokinetic studies to assess metabolism of daidzin to equol during the period of lactation
Valerian (*Valeriana officinalis* L.) root extract [8057-49-6], Valerian oil [8008-88-6]	NIEHS	• Use as a dietary supplement • Lack of toxicological data • Concern for adverse developmental and reproductive effects	• Chemical characterization short-term *in vivo* toxicity screening assays for multiple valerian preparations • Subchronic toxicity and developmental and reproductive toxicity studies including neurotoxicity assessments • Carcinogenicity studies

Evaluation

In carrying out its mission, the NTP provides toxicological evaluations on substances of public health concern. The NTP can initiate bioassays to characterize potential carcinogenicity of only a small fraction of the thousands of substances for which there is little or no information. Many more substances are also studied to assess a variety of non-cancer health-related effects including, but not limited to, reproductive and developmental toxicities, immunotoxicity, neurotoxicity, and genotoxicity. Other biological parameters are often assessed, such as quantifying the disposition and excretion of substances, identifying and correlating biochemical markers with exposure and metabolism, and examining genetic polymorphisms in human drug metabolizing enzymes to understand the susceptibility of individuals and populations to xenobiotic-induced toxicity.

An NTP project review committee evaluates a study's project plan (e.g., design, methods, hypothesis, etc.). The toxicological evaluation for carcinogenicity generally involves repeated administration of a substance to groups of laboratory animals for up to two years. Many short-term, subchronic studies are designed to provide dose-setting information for longer, chronic exposure studies and to address specific gaps in the toxicology database. The adverse health effects from short- or long-term exposures to different dose levels of a substance are examined by observation, histopathology, and several toxicology endpoints, comparing them with control groups of animals not exposed to the substance. Many substances are also studied using protocols specifically designed to address how the substance causes particular toxic effects. The NTP has specific requirements that testing laboratories comply with the Animal Welfare Act of 1966 and adhere to the principles in the "*Guide for the Care and Use of Laboratory Animals*" (NRC, 1996). General information about the objectives and procedures of NTP study protocols is available on the NTP website (*http://ntp.niehs.nih.gov/go/type*). Current testing status can be found at *http://ntpsearch.niehs.nih.gov/index.html?col=010stat*.

The NTP carries out toxicology and carcinogenesis testing through two primary mechanisms: laboratory studies conducted in contract laboratories (see table 13) and studies conducted via IAGs at agencies (see page 78). In addition to toxicology research on compounds and exposures, the NTP supports developing new techniques and methods to improve the ability to identify and assess potential environmental toxicants and to develop and validate novel and alternative testing methods that will reduce, replace, or refine animal use. The NTP also supports developing improved statistical methods for designing and evaluating the results of toxicology studies.

Table 13: NTP Contracts That Supported NTP Testing Activities in FY 2010

Description	Contractor
Archives and Specimen Repository	Experimental Pathology Labs
Cell Phone Radiation	IIT Research Institute
Chemistry Support	Midwest Research Institute
Chemistry Support	Research Triangle Institute
Chemistry Support (2)	Battelle Memorial
Effects of Chemicals in Developing Animals	Research Triangle Institute
Evaluation of Test Agents in Laboratory Animals	Battelle Memorial
Evaluation of Test Agents via Inhalation Exposure	Battelle Memorial
Evaluate Toxicological Potential of Test Agents	Battelle Memorial
Inhalation Toxicology	Alion Science & Technology
Investigative Research Support Contract	Integrated Laboratory Systems
NTP Computer and Statistical Support	Constella
NTP Computing and CEBS Support	Vistronix, Inc.
NTP Information Systems Support	Z-Tech Corporation
NTP Information Systems Support	SciMetrika
NTP Technical Reports Preparation Service	Biotechnical Services
Preparation of Background and Nomination Information	Integrated Laboratory Systems
Perform Cell Dose Response Standard Curves	Hemogenix, Inc
Provantis Software for NTP	INSTEM LSS
Quality Assessment/Pathology Support	Experimental Pathology Labs
Quality Assessment Reports for Audits and Inspections	Dynamac
Statistical Support Services	SRA International, Inc.
Therapeutic Agents to Induce Immunotoxicity	Virginia Commonwealth University

Review and Dissemination

The results of toxicology and carcinogenesis studies undergo rigorous peer review and are published in several NTP report series:

- Technical Reports (TR). This series presents the results of long-term, generally 2-year, toxicology and carcinogenicity studies, typically conducted in rats and mice. Results of genetic toxicology, absorption, distribution, metabolism, and excretion (ADME), and toxicokinetic studies are often included in the reports. The Technical Reports Review Subcommittee of the NTP BSC (see Advisory Boards and Committees, page 8) evaluates the draft reports at a public meeting. Starting in 2011, the draft reports will be reviewed by *ad hoc* expert panels.

- NTP Toxicity (TOX) Reports. TOX reports are prepared for studies where the substance exposure period is short term, generally up to 13 weeks. Draft reports are typically peer reviewed by letter review.

- Genetically Modified Models (GMM) Reports. NTP began the GMM report series in May 2003. This report series presents the results of substances evaluated by NTP in transgenic mouse strains (e.g., p53+/- heterozygous and Tg.AC mice). Starting in 2011, the draft reports will be reviewed by *ad hoc* expert panels.

Abstracts of the TR, TOX, and GMM series are posted on the NTP website, and PDF files of completed reports are available at the NTP website (*http://ntp.niehs.nih.gov/go/reports*) and are also catalogued in PubMed. Pathology data from the NTP rodent studies included in these reports undergo several reviews. The final review is by a pathology working group (PWG), a panel of experts convened by the NTP to review the microscopic evaluations. After the NTP PWG review, pathology tables and body weight and survival graphs for the completed studies are made publicly available (*http://ntp.niehs.nih.gov/go/peerreview*) until draft study reports are completed for peer review.

When the draft reports are completed for peer-review, the abstracts are put on the NTP website with the list of reports. The pathology tables and the body weight and survival graphs are accessible at the end of the abstract text. Following peer review, the NTP finalizes the report, posts it on its website (*http://ntp.niehs.nih.gov/go/reports*) and provides electronic links to the final pathology tables and the curves for body weight and survival. Study summaries for other types of studies, such as immunotoxicity, developmental toxicity, and reproductive toxicity studies, are also available on the "NTP Study Reports" page on the website.

Chronic Toxicity/Carcinogenicity Studies

In the area of general toxicology assessments, the scope and types of studies performed are dictated mainly by the data needs for the specific substance being studied. General toxicology studies usually fall into two categories: subchronic or pre-chronic studies, and 2-year chronic toxicology and carcinogenicity studies. Two-year studies in rodents are a method by which chemicals or physical agents are identified as having the potential to be hazardous to humans.

The chronic toxicology and carcinogenicity studies in conventional rodent models generally use both male and female rats (Fischer 344/N, Harlan Sprague Dawley, or Wistar Han) and mice (B6C3F1 hybrid), with three exposure levels plus untreated controls, in groups of 50 animals, for two years; other rodent models (e.g., genetically modified mice) are used as needed. If adequate data exist in the literature for one rodent species (rats or mice), then typically only the remaining species is studied. The NTP interfaces its testing with regulatory agencies and the private sector to minimize duplication of effort. Studies ongoing, initiated, completed, and published in FY 2010 are listed in Tables 14, 15, 16, and 17, respectively.

The NTP describes the results of individual experiments on a chemical agent and notes the strength of evidence for conclusions of each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than do control animals, do not necessarily mean that a chemical is not a carcinogen, because the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential to be hazardous to humans.

Table 14: Chronic Toxicity/Carcinogenicity Studies Ongoing During FY 2010

Study	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Acrylamide	[79-06-1]	Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Water	2 years	Beland
Aging cohort study - 129/SvlmJ mouse		Mice: 129S1/SvlmJ	Not applicable	2 years	French
Aging cohort study - B6C3F1J mouse		Mice: B6C3F1 (Jackson)	Not applicable	2 years	French
Aging cohort study - C3H/HeJ mouse		Mice: C3H/HeJ	Not applicable	2 years	French
Aging cohort study - C57/BL/6J mouse		Mice: C57BL/6J (Jackson)	Not applicable	2 years	French
Aging cohort study - CAST/EiJ mouse		Mice: CAST/EiJ (M. m. castaneus)	Not applicable	2 years	French
Aging cohort study - NZO/HiLtJ mouse		Mice: NZO/HiLtJ	Not applicable	2 years	French
Aging cohort study - PWK/PhJ mouse		Mice: PWK/PhJ	Not applicable	2 years	French
Aging cohort study - WSB/EIJ mouse		Mice: WSB/EiJ (M. m. domesticus)	Not applicable	2 years	French
Aging cohort study – A/J mouse		Mice: A/J	Not applicable	2 years	French
Aging cohort study - NOD. B10Sn-H2(b)/J		Mice: NOD. B10Sn-H2(b)/J	Not applicable	2 years	French
Aloe vera whole leaf extract (native)		Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Water	2 years	Boudreau
Antimony trioxide	[1309-64-4]	Rats: Wistar Han Mice: B6C3F1	Inhalation	2 years	Stout
3′-Azido-3′-deoxythymidine (AZT)	[30516-87-1]	Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Gavage	2 years	Beland
*3′-Azido-3′-deoxythymidine (AZT)	[30516-87-1]	Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Gavage	9 months	Leakey
AZT/drug combinations transplacental/ neonatal study		Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Gavage	2 years	Beland
AZT/drug combinations transplacental carcinogenesis study		Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	*In utero*	2 years	Beland
2,3-Butanedione (diacetyl)	[431-03-8]	Rats: Wistar Han Mice: B6C3F1	Inhalation	2 years	Morgan

Study	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Cobalt	[7440-48-4]	Rats: F344/NTac Mice: B6C3F1	Inhalation	2 years	Hooth
Dibutyl phthalate	[84-74-2]	Rats: Harlan SD Mice: B6C3F1	Feed	2 years	Blystone
N,N-Dimethyl-p-toluidine	[99-97-8]	Rats: F344/N	Gavage	2 years	Dunnick
Furan	110-00-9	Rats: F344 (NCTR) Mice: B6C3F1	Gavage	2 years	Beland
Ginkgo biloba extract	[90045-36-6]	Rats: F344/N Mice: B6C3F1	Gavage	2 years	Chan
Glycidamide	[5694-00-8]	Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Water	2 years	Beland
Green tea extract		Rats: Wistar Han Mice: B6C3F1	Gavage	2 years	Chan
2-Hydroxy-4-methoxybenzophenone	[131-57-7]	Rats: Harlan SD Mice: B6C3F1	Feed	2 years	Auerbach
Indole-3-carbinol	[700-06-1]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Gavage	2 years	Wyde
Kava kava extract	[9000-38-8]	Rats: F344/N Mice: B6C3F1	Gavage	2 years	Behl/Chan
Metalworking fluids (CIMSTAR 3800)		Rats: Wistar Han Mice: B6C3F1	Inhalation	2 years	Morgan
Metalworking fluids (Trim VX)		Rats: Wistar Han Mice: B6C3F1	Inhalation	2 years	Morgan
Methyl *trans*-styryl ketone	[1896-62-4]	Rats: F344/N Mice: B6C3F1	Topical application	2 years	Cunningham
Pentabromodiphenyl oxide (technical) (DE 71)	[32534-81-9]	Rats: Wistar Han Mice: B6C3F1	Gavage	2 years	Dunnick
PFOA	[335-67-1]	Rats: Harlan SD	Feed	2 years	Blystone
PFOA	[335-67-1]	Rats: Harlan SD	Feed	2 years	Blystone
beta-Picoline	[108-99-6]	Rats: F344/N Mice: B6C3F1	Water	2 years	Wyde
Pyrogallol	[87-66-1]	Rats: F344/N Mice: B6C3F1	Topical application	2 years	Mercado-Feliciano
All-*trans*-retinyl palmitate	[79-81-2]	Mice: SKH-1 Hairless	Topical application	1 year	Boudreau
Styrene-acrylonitrile trimer		Rats: F344/N	Feed	2 years	Behl/Chhabra
Tetrabromobisphenol A	[79-94-7]	Rats: Wistar Han Mice: B6C3F1	Gavage	2 years	Dunnick
alpha/beta-Thujone mixture	[76231-76-0]	Rats: F344/N Mice: B6C3F1	Gavage	2 years	Hooth
Trimethylolpropane triacrylate	[15625-89-5]	Rats: F344/N Mice: B6C3F1	Topical application	2 years	Surh/Chhabra
Tripelennamine Hydrochloride	[154-69-8]	Rats:F344/N Mice: B6C3F1	Feed	11 months	Jackson
Vinylidene chloride	[75-35-4]	Rats: F344/N Mice: B6C3F1	Inhalation	2 years	Wyde
Bromodichloroacetic acid (water disinfection byproduct)	[71133-14-7]	Rats: F344/NTac Mice: B6C3F1	Water	2 years	Hooth
Zinc carbonate, basic	5263-02-5	Rats: Harlan SD	Feed	2 years	Wyde

Table 15: Chronic Toxicity/Carcinogenicity Studies Initiated During FY 2010					
Study	**[CASRN]**	**Species/Strain**	**Route**	**Study Length**	**Project Leader**
Aging Cohort Study – CAST/EiJ mouse		Mice: CAST/EiJ *(M. m. castaneus)*	Not applicable	2 years	French
Aging Cohort Study - NZO/HiLtJ mouse		Mice: NZO/HiLtJ	Not applicable	2 years	French
Aging Cohort Study - PWK/PhJ mouse		Mice: C3H/HeJ	Not applicable	2 years	French
Aging Cohort Study - C57/BL/6J mouse		Mice: PWK/PhJ	Not applicable	2 years	French
Aging Cohort Study - WSB/EIJ mouse		Mice: WSB/EIJ *(M. m. domesticus)*	Not applicable	2 years	French
Aging Cohort Study - NOD. B10Sn-H2(b)/J		Mice: NOD. B10Sn-H2(b)/J	Not applicable	2 years	French
Dibutyl phthalate	84-74-2	Rats: Harlan SD, Mice:B6C3F1	Feed	2 years	Blystone
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats:Harlan Sprague-Dawley, Mice: B6C3F1	Feed	2 years	Auerbach

Table 16: Technical Reports Completed During FY 2010

Chemical/Exposure–Study Type	[CASRN]	Technical Report Number	Use
1-Bromopropane	[106-94-5]	TR-564	Primarily used as an intermediate in the production of pesticides, quaternary ammonium compounds, flavors and fragrances, pharmaceuticals, and other chemicals in well-controlled, closed processes. Also used as a less toxic replacement for methylene chloride in vapor and immersion degreasing. Also introduced as a solvent for adhesive resins, and has been marketed as a replacement for ozone depleting refrigerants.
bis(2-Chloroethoxy) methane	[111-91-1]	TR-536	Used as a solvent and the starting agent in the production of fungicides and polysulfide polymers.
Diethylamine	[109-89-7]	TR-566	Used as a chemical intermediate to produce the corrosion inhibitor *N,N*-diethylethanolamine and a lesser amount is used to produce pesticides and insect repellants and in rubber processing.
Ginseng	[50647-08-0]	TR-567	A perennial aromatic herb widely used in herbal remedies, dietary supplements, cosmetics, and as a food additive.
Milk thistle extract	[84604-20-6]	TR-565	Used as an herbal supplement and medicinally as an hepatoprotectant and for treatment of chronic inflammatory liver disorders.
Pulegone	[89-82-7]	TR-563	Major constituent of oil of pennyroyal. Used for flavoring foods and drinks. Pennyroyal oil has been used as a fragrance agent and as an herbal medicine.

Table 17: Technical Reports Published During FY 2010

Chemical/Exposure–Study Type	[CASRN]	Technical Report Number	Use
Dibromoacetonitrile Drinking Water – toxicology and carcinogenesis	[3252-43-5]	TR-544	Dibromoacetonitrile is formed as a result of the reaction of chlorine oxidizing compounds (e.g., chlorine gas, hypochlorous acid, and hypochlorite) with natural organic matter, particularly nitrogen-containing organic compounds, in water containing bromine; it is also a by-product of ozone disinfection. Dibromoacetonitrile is not produced on a large industrial scale. Thus, chlorinated drinking water is the primary source of human exposure to dibromoacetonitrile.
Ethinyl Estradiol Feed – multigenerational reproductive toxicology	[57-63-6]	TR-547	Ethinyl estradiol is a potent synthetic estrogen widely used in pharmaceutical preparations. Its high potency and widespread use led to its selection by the National Toxicology Program for inclusion in studies to examine endocrine disrupting compounds with estrogenic activity, both because of its utility as a positive control to which weaker estrogens can be compared and because of potential human developmental exposures resulting from unintentional continuation of the use of oral contraceptives containing ethinyl estradiol during early pregnancy.
Ethinyl Estradiol Feed – toxicology and carcinogenesis	[57-63-6]	TR-548	Ethinyl estradiol is a potent synthetic estrogen widely used in pharmaceutical preparations. Its high potency and widespread use led to its selection by the National Toxicology Program for inclusion in studies to examine endocrine disrupting compounds with estrogenic activity, both because of its utility as a positive control to which weaker estrogens can be compared and because of potential human developmental exposures resulting from unintentional continuation of the use of oral contraceptives containing ethinyl estradiol during early pregnancy.

Only summaries of carcinogenic activity conclusions are included in the tables.
Complete information is available in the full study reports found at *http://ntp.niehs.nih.gov/*.

Levels of Evidence of Carcinogenic Activity			
Male Rats	Female Rats	Male Mice	Female Mice
Some evidence	Clear evidence	No evidence	Clear evidence
No evidence	No evidence	No evidence	No evidence
No evidence	No evidence	No evidence	No evidence
No evidence	No evidence	No evidence	No evidence
No evidence	No evidence	No evidence	No evidence
No evidence	Some evidence	Clear evidence	Clear evidence

Levels of Evidence of Carcinogenic Activity			
Male Rats	Female Rats	Male Mice	Female Mice
Clear evidence	Some evidence	Clear evidence	Clear evidence

Ethinyl estradiol administered at exposure concentrations of 2, 10, or 50 ppb in a low phytoestrogen diet to NCTR CD (SD) rats showed clear biological activity including potentially adverse effects. Both preweaning and postweaning body weights of males and females were decreased during periods of direct exposure to dosed feed. Ethinyl estradiol accelerated the attainment of puberty of females under continuous exposure conditions (F_1 and F_2) and of animals where dosing was terminated at weaning (F_3). Perturbation of the estrous cycle (prolonged cycles, aberrant cycles, time in estrus) in young females after vaginal opening and prior to mating was observed in the F_1 and F_2 generations. In males, statistically significant inductions of male mammary gland hyperplasia (F_0 through F_3 generations) and mild mineralization of renal tubules (F_1 and F_2 generations) were observed. The majority of these effects were observed at 50 ppb, but significant effects on body weight reduction and male mammary gland hyperplasia were observed at the lowest exposure concentration (2 ppb). With the possible exception of a 1.5-day delay of preputial separation in the F_2 males, effects of ethinyl estradiol did not appear to be magnified across exposed generations.

- Under the conditions of this 2-year feed study with continuous exposure to the test compound from conception through termination (F_1C), there was *no evidence of carcinogenic activity* of ethinyl estradiol in male or female SD rats exposed to 2, 10, or 50 ppb.
- Under the conditions of this 2-year feed study with exposure to the test compound from conception through 20 weeks followed by control feed until termination (F_1T140), there was *no evidence* of carcinogenic activity of ethinyl estradiol in male SD rats exposed to 2, 10, or 50 ppb. There was *equivocal evidence* of carcinogenic activity of ethinyl estradiol in female SD rats based on marginally increased incidences of uterine stromal polyps.
- Under the conditions of this study where offspring of two prior generations of animals exposed to ethinylestradiol in feed were exposed from conception through weaning (PND 21), followed by control feed through termination (F_3T21), there was equivocal evidence of carcinogenic activity of ethinyl estradiol in male SD rats based on increased incidences of preputial gland epithelial neoplasms and a marginal increased incidence of mammary gland adenoma or adenocarcinoma (combined). There was *equivocal evidence* of carcinogenic activity of ethinyl estradiol in female SD rats based on marginally increased incidences of uterine stromal polyps.

CLEAR Evidence SOME Evidence EQUIVOCAL Evidence NO Evidence

Table 17: Technical Reports Published During FY 2010

Chemical/Exposure–Study Type	[CASRN]	Technical Report Number	Use
Isoeugenol Gavage – toxicology and carcinogenesis	[97-54-1]	TR-551	Isoeugenol is one of several structurally similar phenylpropenoid compounds produced by plants. It has been extracted from calamus, savory, basil, ylang-ylang, clove, tuberose, jonquil, nutmeg, tobacco, sandalwood, dill seed, mace, gardenia, petunia, and other flowers. Isoeugenol can also be produced by isomerization of eugenol, which occurs naturally in clove, pimento, bay leaf, and cinnamon. Isoeugenol is incorporated into numerous household and personal hygiene products, including perfumes, cream lotions, soaps, and detergents. As a flavoring agent, isoeugenol is added to nonalcoholic drinks, baked foods, and chewing gums.
Aloe Vera SSL and Topical – Photocarcinogenesis	[481-72-1]	TR-553	The popular recognition of the *Aloe barbadensis* Miller *(Aloe vera)* plant as a therapeutic dermatologic agent has led to the widespread incorporation of *Aloe vera* leaf extracts in skincare products. Studies have suggested that *Aloe vera* in skincare preparations may enhance the induction of skin cancer by ultraviolet radiation. A 1-year study was conducted in mice to determine whether the topical application of creams containing *Aloe vera* plant extracts (*aloe* gel, whole leaf, or decolorized whole leaf) or creams containing *aloe*-emodin would enhance the photocarcinogenicity of SSL.
5-(Hydroxymethyl)-2-furfural Gavage – toxicology and carcinogenesis	[67-47-0]	TR-554	5-(Hydroxymethyl)-2-furfural is formed when reducing sugars such as fructose and sucrose are heated in the presence of amino acids. 5-(Hydroxymethyl)-2-furfural is ubiquitous in the human diet and occurs at concentrations greater than 1 g/kg in dried fruits, caramel products, certain types of fruit juices, and up to 6.2 g/kg in instant coffee. It also occurs naturally and has been identified in honey, apple juice, citrus juices, beer, brandy, milk, breakfast cereal, baked foods, tomato products, and home cooking of sugar and carbohydrates. Industrially, 5-(hydroxymethyl)-2-furfural is used in the synthesis of dialdehydes, glycols, ethers, aminoalcohols, acetals, and phenol/furfural novolak-type resins.
1,2-Dibromo-2,4-dicyanobutane Dermal – toxicology and carcinogenesis	[35691-65-7]	TR-555	1,2-Dibromo-2,4-dicyanobutane is used in cosmetics and other household products and is widely used as a component of numerous over-the-counter health care products.
Chromium Picolinate Monohydrate Feed – toxicology and carcinogenesis	[27882-76-4]	TR-556	Chromium picolinate monohydrate is the commercially available form of chromium picolinate. Chromium picolinate is one of a number of compounds that contain chromium in the trivalent state (Cr III), which is the predominant form of chromium in nature. Humans ingest Cr III in food and dietary supplements. The major uses of Cr III in the chemical and manufacturing industries include production of chromium pigments and leather tanning.
Androstenedione Gavage – toxicology and carcinogenesis	[63-05-8]	TR-560	Androstenedione is an androgen steroid that is normally synthesized within men and women and may be metabolized to a more potent androgen or estrogen hormone.
Goldenseal Root Powder Feed – toxicology and carcinogenesis		TR-562	Goldenseal root powder is used in folk medicine for the treatment of gastrointestinal disturbances, urinary disorders, hemorrhage, skin, mouth, and eye infections, and inflammation. The major alkaloids in goldenseal are berberine, hydrastine, and canadine.

Only summaries of carcinogenic activity conclusions are included in the tables. Complete information is available in the full study reports found at *http://ntp.niehs.nih.gov/*.

Levels of Evidence of Carcinogenic Activity			
Male Rats	Female Rats	Male Mice	Female Mice
Equivocal evidence	No evidence	Clear evidence	Equivocal evidence

These experiments investigated the potential of topical application of creams containing extracts of *Aloe barbadensis* Miller plant (*aloe* gel, whole leaf, or decolorized whole leaf) or *aloe*-emodin to alter the photocarcinogenic activity of filtered xenon arc SSL in male and female SKH-1 hairless mice. Data on skin lesions were collected both on digital images during the in-life phase and by histopathologic evaluation at necropsy. No effects of creams upon SSL-induced skin lesions were identified from data collected during the in-life phase.
***Aloe* Gel or *Aloe*-emodin:** Under the conditions of these studies, there was a weak enhancing effect of *aloe* gel or *aloe*-emodin on the photocarcinogenic activity of SSL in female but not in male SKH-1 mice based on an increase in the multiplicity of histopathologically determined squamous cell neoplasms. *Aloe* Whole Leaf or Decolorized Whole Leaf: Under the conditions of these studies, there was a weak enhancing effect of *aloe* whole leaf or decolorized whole leaf on the photocarcinogenic activity of SSL in both male and female SKH-1 mice based on an increase in the multiplicity of histopathologically determined squamous cell neoplasms.

No evidence	No evidence	No evidence	Some evidence
No evidence	No evidence	No evidence	No evidence
Equivocal evidence	No evidence	No evidence	No evidence
Equivocal evidence	Equivocal evidence	Clear evidence	Clear evidence
Clear evidence	Clear evidence	Some evidence	No evidence

CLEAR Evidence SOME Evidence EQUIVOCAL Evidence NO Evidence

The NTP anticipates that six Technical Reports will undergo peer review in FY 2010, as shown in Table 18.

Table 18: Technical Reports expected to undergo peer review in FY 2011

Chemical	Technical [CASRN] Number	Report	Use
Acrylamide Inhalation	[79-06-1]	TR-575	Acrylamide, a water-soluble α,β-unsaturated amide, is a contaminant in baked and fried starchy foods, including French fries, potato chips, and bread, as a result of Maillard reactions involving asparagine and reducing sugars. Additional sources of acrylamide exposure include cigarettes, laboratory procedures involving polyacrylamide gels, and various occupations (e.g, monomer production and polymerization processes).
AIDS Therapeutics: 3′-Azido-3′-Deoxythymidine (AZT) Lamivudine (3TC) Nevirapine (NVP) Melfinavir Misylate (NFV)	 [30516-87-1] [134678-17-4] [129617-40-2] [159989-65-8]	TR-569	With the increased administration of multidrug regimens to pregnant women who are HIV-1 positive, along with the increased efficacy of these combinations, determining the long-term consequences of the antiretroviral agents in noninfected children becomes important. The goal of the current study was to determine the carcinogenicity of combinations of antiretroviral drugs in male and female B6C3F1 mouse pups exposed transplacentally and monitored for 2 years. • **AZT** was synthesized initially for use as an anticancer agent and was later reported to block the infectivity and cytopathic effects, *in vitro*, of human immunodeficiency virus type-1 (HIV-1), due to the inhibition (by AZT 5′-triphosphate) of viral reverse transcriptase. Pregnant women who are positive for HIV-1 are given AZT to manage the infection and to prevent maternal-to-fetal transmission of the virus. • **3TC** was synthesized initially as a racemate and then in enantiomerically pure forms. 3TC (as 3TC 5′-triphosphate) is thought to inhibit viral reverse transcriptase by competing with deoxycytidine 5′-triphosphate for incorporation into HIV-1 DNA. When used for the management of HIV-1 infections, 3TC is always used in combination with another nucleoside reverse transcriptase inhibitor (e.g., AZT) and either a protease inhibitor (e.g., nelfinavir mesylate, NFV) or a non-nucleoside reverse transcriptase inhibitor (e.g., nevirapine, NVP). • **NVP** a non-nucleoside reverse transcriptase inhibitor, was first synthesized in 1991. NVP inhibits HIV-1 reverse transcriptase noncompetitively by binding to an allosteric site on the enzyme; this action is specific for HIV-1 reverse transcriptase. NVP is usually given as part of a three-drug regimen. Typical regimens in adults and adolescents include NVP and 3TC or emtricitabine and AZT or tenofovir. • **NFV** synthesis was reported in 1997. NFV acts by inhibiting HIV-1 protease, the enzyme responsible for cleavage of the polyprotein resulting from the gag and gag-pol genes of HIV-1. This inhibition results in an immature, noninfectious virus. NFV is always used in combination with other antiretroviral agents, typically two nucleoside reverse transcriptase inhibitors (e.g., AZT and 3TC).



Chemical	[CASRN]	Report	Use
A Nondecolorized Whole Leaf Extract of *Aloe barbadensis* Miller (*Aloe* Vera)		TR-577	*Aloe barbadensis* Miller *(Aloe vera)* has enjoyed a long history of lay acceptance as an herbal remedy and is perhaps the most popular herbal remedy in use today. In recent times, the oral consumption of *Aloe vera* has been promoted as a prophylaxis and treatment to alleviate a variety of unrelated systemic conditions.
α,β-Thujone	[76231-76-0]	TR-570	Thujone is a monoterpene ketone that exists in two stereoisomeric forms (-)-3-isothujone, or α-thujone, and (+)-3-thujone, or β-thujone. Thujone occurs in nature as a mixture of α- and β-isomers and is the primary constituent of essential oils derived from a variety of plants. Although thujone itself is banned as a food additive in the United States, it appears in many other natural flavoring substances that are approved food additives and flavorings.
Kava Kava Extract	[9000-38-8]	TR-571	Kava beverages, made from dried roots of the shrub *Piper methysticum*, have been used ceremonially and socially in the South Pacific and in Europe since the 1700s. The drink is reported to have pleasant mild psychoactive effects, similar to alcoholic beverages. In the United States, kava kava is an herbal product used extensively as an alternative to anti-anxiety drugs such as Xanax® and Valium.®
Methyl *trans*-Styryl Ketone	[1896-62-4]	TR-572	Methyl *trans*-styryl ketone is used as a synthetic flavoring agent and a fragrance additive in food and personal care products.
Retinoic Acid (RA) Retinyl Palmatate (RP)	[302-79-4] [79-81-2]	TR-568	Topical retinoids, compounds that are metabolites, analogs, or derivatives of retinol and possess biological vitamin A activity, are among the most used adjunctive agents for the mitigation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of photodamaged and chronically aged skin. RA is the most active biological form of vitamin A and remains the medical treatment of choice for photoaged skin. RA is the major storage form of vitamin A in the skin and, because RP is also the most stable of available vitamin A esters, it is readily incorporated into the oil phase of cosmetic creams or lotions. Therefore, the topical application of RP is a practical strategy for increasing the levels of vitamin A in the skin.
Styrene-acrylonitrile (SAN) Trimer		TR-573	Styrene-acrylonitrile trimer is a byproduct of the production of acrylonitrile styrene plastics and is created in specific manufacturing processes for polymers of acrylonitrile and styrene.

General Toxicology Studies

The NTP performs prechronic toxicity studies to address specific deficiencies in toxicology databases for chemicals, such as an understanding of toxicity with repeated exposures; to identify target organs for more in-depth systems toxicology evaluations and mechanistic studies; and to provide dose-setting information for possible chronic studies.

Although designs are flexible, prechronic studies usually involve exposures of rats and mice of both sexes to substances for periods of 14-90 days. Assessments almost always include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. The frequency of malformed red blood cells (micronucleated erythrocytes, a measure of chromosomal damage) is determined as an *in vivo* measure of genotoxic potential.

The study protocol may include more detailed or focused studies when findings published in the existing scientific literature or identified in initial NTP studies suggest a target organ or system. The study protocol may include separate studies of reproductive, genetic, or immunological toxicity based on the outcome of the toxicity screens and may use additional endpoints to improve our understanding of the mechanisms and modes of action of a chemical.

In some cases, the NTP uses alternative models, including genetically modified mouse models and non-mammalian models, for prechronic studies. Such studies are presented in the section "Genetic and Alternative Test Systems" (page 72). Tables 19-21 list the toxicity studies that were ongoing, initiated, and completed, respectively, during FY 2010. Information is available at *http://ntp.niehs.nih.gov/go/reports*. Table 22 lists toxicity studies planned for FY 2011.

Table 19: Ongoing Prechronic Toxicity Studies During FY 2010

Study	[CASRN]	Species/Strain	Study Route	Length	Project Leader
*3′-Azido-3′-deoxythymidine (AZT)	[30516-87-1]	Mice: P53 +/- (FVB/N)	Gavage	9 months	Leakey
Glucosamine hydrochloride + chondroitin sulfate	[9007-28-7] [66-84-2]	Rats: Zucker – Obese (HsdHlr: ZUCKER-Leprfa) Rats: Zucker - Lean (HsdHlr: ZUCKER-Lepr+)	Gavage	13 weeks	Leakey
Microcystin-LR (TGMX)	[101043-37-2]	Rats: Wistar Han	Intravenous	1/2/6/24 hours	Walker
Pregnancy rate comparison study		Rats: Harlan SD (Indianapolis Facility), Rats: Harlan SD (Dublin Facility)	Not applicable	16 weeks	Vallant
QT drugs (bepridil hydrochloride)	[74764-40-2]	Dog: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (diltiazem hydrochloride)	[33286-22-5]	Dog: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (loratadine)	[79794-75-5]	Dog: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (lovastatin)	[75330-75-5]	Dog: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (sotalol hydrochloride)	[959-24-0]	Dog: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (terfenadine)	[50679-08-8]	Dog: Beagles	Oral (capsule)	1 day	Hooth
Sodium tungstate, dihydrate	10213-10-2	Rats: Harlan SD Mice: B6C3F1	Water	13 weeks	Hooth
tris(2-Chloroisopropyl)phosphate	13674-84-5	Rats: Harlan SD Mice: B6C3F1	Feed	90 days	Stout
Usnea lichen		Rats: F344 (NCTR) Mice:B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Feed	90 days 2 weeks	Leakey
(+)-Usnic acid	[7562-61-0]	Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Feed	2 weeks 90 days	Leakey

Table 20: Toxicity Studies Initiated during FY 2010

Chemical	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Bisphenol A	[80-05-7]	Rats: SD (NCTR)	Gavage	90 days	Delclos
Black cohosh	[84776-26-1]	Mice: B6C3F1	Gavage	90 days	Mercado-Feliciano
bis(2-Chloroethoxy)methane	[111-91-1]	Mice: C57BL/6J (Jackson) Mice: C3H/HeJ	Gavage	10 days, 3 days	Dunnick
Ephedrine + caffeine combination		Mice: C57BL/6J (Jackson) Mice: C3H/HeJ, Mice:C3H/HeJ	Gavage	10 days, 3 days	Dunnick
Insertional mutagenesis (Radiation Levels)		Mice:B6.SJL-Ptprc[a] Pepc[b]/BoyJ	Whole-body exposure	8 weeks	Irwin
Insertional mutagenesis II (SIN vector)		Mice: B6.SJL-Ptprc[a] Pepc[b]/BoyJ, Mice: B6.SJL-Ptprc[a] Pepc[b]/BoyJ	Intravenous	8 plus 3 weeks	Irwin
2,3-Pentanedione	[600-14-6]	Rats: Wistar Han Mice: B6C3F1	Inhalation	90 days	Morgan

Table 21: Toxicity Studies Completed during FY 2010

Chemical	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Abrasive blasting agents (blasting sand)		Rats: Harlan SD Rats:F344/NTac	Inhalation	39 weeks, 14 days	Roycroft
Abrasive blasting agents (specular hematite)		Rats: Harlan SD Rats: F344/NTac	Inhalation 14 days	39 weeks,	Roycroft
Acetoin	[513-86-0]	Rats: Wistar Han Mice:B6C3F1	Inhalation	90 days, 14 days	Morgan
Cell phone radiation (code division multiple access [CDMA])		Rats: Harlan SD Mice: B6C3F1	Whole-body	5 days, 49 days	Wyde
Cell phone radiation (global systems mobile [GSM])		Rats:Harlan Sprague-Dawley, Mice: B6C3F1	Whole-body exposure	49 days 5 days	Wyde
p-Chloro-a,a,a-trifluorotoluene	[98-56-6]	Rats: Harlan SD Mice: B6C3F1	Inhalation	90 days	Stout
Glucosamine	[3416-24-8]	Rats: Zucker - Obese (HsdHlr:ZUCKER-Leprfa) Rats: Zucker - Lean (HsdHlr:ZUCKER-Lepr+)	Gavage	13 weeks	Leakey
Gum guggul extract		Rats: Harlan SD Mice: B6C3F1	Gavage	13 weeks	Wyde
Insertional mutagenesis II (SIN vector)		Mice: B6.SJL-Ptprc[a] Pepc[b]/BoyJ,	Intravenous	8 plus 3 weeks	Irwin
Ionic liquid toxicity		Rats: Harlan SD Mice: B6C3F1	Water	14 days	Hooth
2-Methoxy-4-nitroaniline	[97-52-9]	Rats: Harlan SD Mice: B6C3F1	Feed	Range finding, 14 days	Surh
Myristicin	[607-91-0]	Rats: F344/NTac Mice:B6C3F1	Gavage	13 weeks	Wyde
Resveratrol	[501-36-0]	Rats: Wistar Han, Rats: F344/NTac, Mice: B6C3F1	Gavage	2 weeks, 13 weeks	Germolec
Serotype 5 adeno-associated viral vector (rAAV5SCTLA4:Ig)		Mice: BALB/c	Intraductal cannulation	13 weeks	Irwin
Vincamine	[1617-90-9]	Mice B6C3F1	Gavage	2 weeks	Chan

Table 22: Toxicity Studies Planned for FY 2011*					
Chemical	**[CASRN]**	**Species/Strain**	**Route**	**Study Length**	**Project Leader**
3-Aminopyridine	[462-08-8]	Rats: F344/NTac Mice: B6C3F1	Gavage	14 days	Dunnick
2-Aminopyridine	[504-29-0]	Rats: F344/NTac Mice: B6C3F1	Gavage	14 days	Dunnick
4-Aminopyridine	[504-24-5]	Rats: F344/NTac Mice: B6C3F1	Gavage	14 days	Dunnick
Comparison study of aminopyridines/ troponin levels		Rats: F344/NTac Mice: B6C3F1	Gavage	1 & 4 hours	Dunnick
Microcystin mixture (TGMX)		Rats: Wistar Han	Intravenous	1/2/6/24 hours	Walker
Pyridine	[110-86-1]	Mice: B6C3F1	Gavage	14 days	Dunnick
Serotype 2 adeno-associated viral vector hAQP1 (rAAV2hAQP1)		Mice: BALB/c	Intraductal Cannulation	13 weeks	Irwin

** Known test articles as of 10/1/2010. Others may be scheduled as protocols are finalized.*

Mutagenesis and Genetic Toxicity

Genetic toxicity test results are used to help interpret toxicity, carcinogenicity, or other *in vivo* test results and to provide a database for use in structure-activity analyses. Analysis of the early, multi-test database showed that positive results for a chemical in the *Salmonella* gene mutation assay were sometimes correlated with carcinogenicity in several species/sexes of rodents and at several tissue sites. Subsequently, studies of the correlation between mutagenicity test data and rodent carcinogenicity showed a strong association between clearly positive results in long-term mouse peripheral blood micronucleus tests and rodent carcinogenicity. The importance of genetic toxicity test data in assessing exposure hazard for NTP chemicals is underscored by the fact that most organic chemicals (other than hormones) identified as human carcinogens by the International Agency for Research on Cancer (IARC) are genotoxic, and the vast majority of them are detected by both the *Salmonella* assay and rodent micronucleus tests. Additional assays may be conducted with certain chemicals to gain further insight into the types of DNA and chromosomal damage induced by a chemical. Substances tested for genetic toxicity during FY 2010 are listed in Table 23. Information is available at (*http://ntp.niehs.nih.gov/go/reports*).

Table 23: Ongoing and Completed Genetic Toxicity Studies During FY 2010		
Chemical	**[CASRN]**	**Testing Battery**
2-Aminoanthracene	[613-13-8]	*Salmonella*
3′-Azido-3′-deoxythymidine (AIDS)	[30516-87-1]	*Salmonella*
Acetoin	[513-86-0]	Micronucleus
Antimony trioxide	[1309-64-4]	Micronucleus
2,6-Diethylaniline (2,6-DEA)	[579-66-8]	*Salmonella*
Dimethylamine borane	[74-94-2]	*Salmonella*
2′,2‴-Dithiobisbenzanilide	[135-57-9]	*Salmonella*
Efavirenz	[154598-52-4]	*Salmonella*
2-Ethylaniline	[578-54-1]	*Salmonella*
3-Ethylaniline	[587-02-0]	*Salmonella*
4-Ethylaniline	[589-16-2]	*Salmonella*
Gum guggul extract		Micronucleus
2-metyl-6-ethylanline	[24549-06-2]	*Salmonella*
Milk thistle extract	[84604-20-6]	*Salmonella*
Nelfinavir	[159989-64-7]	*Salmonella*
Nevirapine	[129618-40-2]	*Salmonella*
ortho-Phthalaldehyde	[643-79-8]	Micronucleus
p-Chloro-a,a,a-trifluorotoluene	[98-56-6]	Micronucleus
p-Toluidine	[106-49-0]	*Salmonella*
Pulegone	[89-82-7]	*Salmonella*
Senna (powdered)	[8013-11-4]	Micronucleus
Senna (powdered)	[8013-11-4]	*Salmonella*
Sennoside B	[128-57-4]	*Salmonella*
Sodium tungstate, dihydrate	[10213-10-2]	Micronucleus
Sodium tungstate, dihydrate	[10213-10-2]	*Salmonella*
Styrene-acrylonitrile trimer	SANTRIMER2	Micronucleus
3TC (AIDS initiative)	[134678-17-4]	*Salmonella*
Thiodiglycolic acid	[123-93-3]	*Salmonella*
m-Toluidine	[108-44-1]	*Salmonella*
tris(2-Chloroisopropyl)phosphate	[13674-84-5]	Micronucleus
4,7,10-Trioxatridecane-1,13-diamine	[4246-51-9]	*Salmonella*
tris(2-Chloroisopropyl)phosphate	[13674-84-5]	Micronucleus
Vincristine sulfate salt	[2068-78-2]	Micronucleus
Zinc carbonate, basic	[5263-02-5]	Micronucleus

Organ System Toxicity

Nervous System, Developmental, and Reproductive Toxicity

Behavioral and neurological alterations in response to deleterious environmental agents often represent the earliest evidence of toxicity. These testing batteries examine the sensory, motor, autonomic, and peripheral nervous systems. The Functional Observational Battery employs observational screening, while the NIEHS test battery uses automated test systems to evaluate the various nervous system components.

As part of its charge to test chemicals of concern for potential toxicity, the NTP evaluates developmental and reproductive toxicity primarily by using teratology and Reproductive Assessment by Continuous Breeding (RACB) study designs (see *http://ntp.niehs.nih.gov/go/33668*). The RACB study design was developed by the NTP to identify potential hazards from toxic effects on male and/or female reproduction, to characterize that toxicity, and to define the dose-response relationships for each compound. The study design has evolved over the years: initially the studies mainly used mice as the test species; now, they use rats almost exclusively. As our knowledge has improved and use of sensitive end points has increased, these advances have been incorporated into revisions of the study design.

Table 24 lists completed and ongoing nervous system, developmental, and reproductive studies during FY 2010, and Table 25 lists studies planned for FY 2011.

Table 24: Ongoing and Completed Organ Systems Toxicity Studies During FY 2010

Chemical	[CASRN]	Species/Strain	Route	Project Leader	Testing Battery
Acrylamide	[79-06-1]	Rats: F344 (NCTR)	Gavage	Beland	Neurotox assessment
Bitter orange		Rats: SD	Gavage	Hansen	Teratology
Bitter orange with caffeine		Rats: SD	Gavage	Hansen	Teratology
Black cohosh	[84776-26-1]	Rats: Harlan SD	Gavage	Mercado-Feliciano	RACB - range-finding
n-Butyl-p-hydroxybenzoate	[94-26-8]	Rats: Harlan SD	Gavage	Blystone	RACB - range-finding
Nonylphenol	[84852-15-3]	Rats: SD (NCTR)	Feed	Newbold, Delclos	Multigenerational
p-Synephrine	[94-07-5]	Rats: SD	Gavage	Hansen	Teratology
Synephrine and caffeine	[94-07-5] [58-08-2]	Rats: SD	Gavage	Hansen	Teratology
3,3′,4,4′-Tetrachloroazobenzene	[14047-09-7]	Rats: Crl:CD (SD)	Gavage	Hooth	Teratology - pre-implantation
3,3′,4,4′-Tetrachloroazobenzene	[14047-09-7]	Rats: Crl:CD (SD)	Gavage	Hooth	Postnatal developmental toxicity
tris(2-Chloroisopropyl)phosphate	[13674-84-5]	Rats: Harlan SD	Gavage	Stout	Prenatal developmental toxicity
Vinclozolin	[50471-44-8]	Rats: Wistar Han	Gavage	Bishop	Modified RACB

Table 25: RACB Studies Planned for FY 2011

Chemical	[CASRN]	Species/Strain	Route
Black cohosh	[84776-26-1]	Rats: Harlan SD	Gavage
Butyl paraben	[94-26-8]	Rats: Harlan SD	Feed
Diisobutyl phthalate	[84-69-5]	Rats: Harlan SD	Feed
4-Methylimidazole	[822-36-6]	Rats: Harlan SD	Feed
Sodium tungstate, dihydrate	[10213-10-2]	Rats: Harlan SD	TBD

Immunotoxicity

NTP immunotoxicity studies address adverse effects on the immune system that may result from exposure to environmental chemicals, biological materials, or therapeutic agents. The identification of substances that have potential to cause injury to the immune system is of considerable public health significance as alterations in immune function can lead to increased incidence of hypersensitivity disorders, autoimmune or infectious disease, or neoplasia. Immunotoxicity caused by exposure to chemicals can be divided into two broad research areas: (1) studies of altered hematopoietic (blood cell development) or other immunologic events associated with exposure of humans and animals to chemicals and (2) studies of immune-mediated hypersensitivity (allergy and autoimmunity) resulting from exposure to environmental chemicals or therapeutics. In the former case, the immune system acts as a passive target (nonspecific) for the foreign substance, and the result may be an increased incidence or severity of infectious disease or neoplasia because of the inability to respond adequately to the invading agent. In hypersensitivity (i.e., allergy), the immune system responds to small molecular weight compounds that bind to host tissue, recognizing the complex as foreign antigen. This immune response to the chemical-host tissue complex may lead to diseases, such as respiratory tract allergies (e.g., asthma, rhinitis) or allergic contact (skin) dermatitis. Autoimmunity, another form of immune-mediated disease, is characterized by an immune response against constituents of the body's own tissues (autoantigens). Table 26 lists completed and ongoing immunotoxicity studies during FY 2010.

Table 26: Ongoing and Completed Immunotoxicity Studies During FY 2010

Chemical	[CASRN]	Species/Strain	Route	Project Leader	Testing Battery
Abrasive blasting agents (blasting sand)		Rats: Harlan Sprague Dawley	Inhalation	Roycroft	Immunosuppression
Abrasive blasting agents (specular hematite)		Rats: Harlan Sprague Dawley	Inhalation	Roycroft	Immunosuppression
Autumn Sunset True Color Concentrate		Mice: CBA/Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
3'-Azido-3'-deoxythymidine (AZT)	[30516-87-1]	Mice: B6C3F1	Gavage	Irwin	Immunosuppression-range finding, developmental
Black cohosh	[84776-26-1]	Mice: B6C3F1	Gavage	Mercado-Feliciano	Immunotoxicity
2,3-Butanedione (diacetyl)	[431-03-8]	Mice: BALB/c	Topical application	Morgan	Hypersensitivity
2,3-Butanedione (diacetyl)	[431-03-8]	Mice: BALB/c	Inhalation	Morgan	Immunosuppression-range finding
tert-Butyl hydroperoxide	[75-91-2]	Mice: BALB/c	Topical application	Chhabra	Hypersensitivity
o-Cresol	[95-48-7]	Mice: BALB/c	Topical application	Chhabra	Hypersensitivity
Dibenz(a,h)anthracene	[53-70-3]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression-range-finding, developmental, immunosuppression-full protocol
1,3-Dichloropropene (Telone II)	[542-75-6]	Mice: B6C3F1	Water	Yang	Immunosuppression-full protocol
Dimethylamine borane	[74-94-2]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Double dark fudge true color concentrate		Mice: CBA/ Ca Jackson	Subcutaneous	Howard	Hypersensitivity range finding
Double fudge concentrate		Mice: CBA/Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity

Chemical	[CASRN]	Species/Strain	Route	Project Leader	Testing Battery
Echinacea purpurea, extract	[90028-20-9]	Mice: B6C3F1	Gavage	Irwin	Immunosuppression-full protocol
Elmiron (sodium pentosanpolysulfate)	[37319-17-8]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression-full protocol
Ethanone, 1-(1,2,3,4,5,6,7, 8-octahydro-2,3,8, 8-tetramethyl-2-naphthalenyl)- (Iso-E Super)	[54464-57-2]	Mice: BALB/c	Topical application	Chan	Hypersensitivity
Genistein	[446-72-0]	Mice: NOD/MrKTac	Gavage	Germolec	Autoimmunity
Gum guggul extract		Mice: B6C3F1	Gavage	Wyde	Immunosuppression-range-finding
Heptachlor	[76-44-8]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Ionic liquid (1-butyl-3-methylimidazolium chloride)	[79917-90-1]	Mice: BALB/c	Topical application	Hooth	Hypersensitivity
Ionic liquid (1-butyl-1-methylimidazolium chloride)	[479500-35-1]	Mice: BALB/c	Topical application	Hooth	Hypersensitivity
Ionic liquid (*n*-butylpyridinium chloride)	[1124-64-7]	Mice: BALB/c	Topical application	Hooth	Hypersensitivity
Ionic liquid (1-ethyl-3-methylimidazolium chloride)	[65039-09-0]	Mice: BALB/c	Topical application	Hooth	Hypersensitivity
Lovastatin	[75330-75-5]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression-range finding
Monoclonal antibody protein therapeutics (CD-4)		Mice: B6C3F1	Intraperitoneal injection	Germolec	Immunosuppression-full protocol
Monoclonal antibody protein therapeutics (CD-8)		Mice: B6C3F1	Intraperitoneal injection	Germolec	Immunosuppression-full protocol
Fullerene-C60 (1 micron)	[99685-96-8]	Mice: B6C3F1 Wistar Han	Inhalation	Walker	Immunosuppression-range finding
Fullerene-C60 (50 nm)	[99685-96-8]	Rats: Wistar Han Mice: B6C3F1	Inhalation	Walker	Immunosuppression-range finding
1,5-Naphthalene diisocyanate	[3173-72-6]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Nelfinavir mesylate	[159989-65-8]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression-full protocol, developmental
Nevirapine	[129618-40-2]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression-full protocol, developmental
Perfluorodecanoic acid	[335-76-2]	Rats: Harlan SD	Gavage	Blystone	Immunosuppression
Phenol	[108-95-2]	Mice: B6C3F1	Water	Germolec	Immunosuppression-full protocol
Resveratrol	[501-36-0]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression-range finding
Rosewood True Color Concentrate		Mice: CBA/Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
Sodium tungstate, dihydrate	[10213-10-2]	Mice: B6C3F1	Water	Hooth	Immunosuppression-full protocol
3,3′,4,4′-Tetrachloroazobenzene	[14047-09-7]	Rats: Sprague Dawley	Gavage	Behl	Immunosuppression-range finding
3,3′,4,4′-Tetrachloroazobenzene	[14047-09-7]	Rats: Crl:CD (SD)	Gavage	Behl	Developmental

Disposition, Metabolism and Toxicokinetic Studies

Complete dosimetry of a chemical or physical agent describes its ADME in the body at differing levels of exposure, over all ages, via several routes of exposure, and under varying genetic backgrounds in humans and test animals. Data from NTP chemical disposition and toxicokinetic studies are used in these studies. Substances evaluated during FY 2010 are listed in Table 27, and studies planned for FY 2011 are listed in Table 28. Most studies are conducted in intact laboratory animals; some require incubating human and rodent tissues (liver slices) with the chemical. This information provides dosimetric data that can be combined with other anatomical, biochemical, and physiological information to develop models based on biochemistry and physiologically based pharmacokinetics. Such models are used increasingly in risk assessment to extrapolate between species, across dose ranges, and across different routes of exposure.

Table 27: Ongoing and Completed Disposition, Metabolism and Toxicokinetic Studies During FY 2010

Chemical	[CASRN]	Species/Strain	Route	Project Leader
Anatase (TiO_2)	[1317-70-0]	Mice: Tg.AC (FVB/N) and FVB/N	Topical application	NCTR
Benzene	[71-43-2]	Mice: • BALB/cByJ • WSB/EiJ *(M. m. domesticus)* • CAST/EiJ *(M. m. castaneus)* • C3H/HeJ • DBA/2 Jackson • BTBR T+ tf/J 2, C57BL/6 • FVB/NJ • KK/HlJ • AKR/J • NZW/LacJ • A/J • NOD/LtJ • B6C3F1 • PWD/PhJ *(M. m. musculus)* • MOLF/EiJ *(M. m. molossinus)* • 129S1/SvImJ	Gavage	Cunningham
2,3-Butanedione	[431-03-8]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Oropharyngeal	Waidyanatha
2,3-Butanedione	[431-03-8]		*In vitro*	Waidyanatha
2-Butene-1,4-diol	[110-64-5]		*In vitro*	NCTR
n-Butyl-p-hydroxybenzoate	[94-26-8]	Rats: Harlan Sprague Dawley	Intravenous	Blystone
Cumene	[98-82-8]	Rats: Fischer 344 Mice: B6C3F1	Gavage	Chan
1,3-Dichloro-2-propanol	[96-23-1]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Gavage	Chan
Di(2-ethylhexyl) phthalate	117-81-7	Monkey: Rhesus	Gavage	Delclos
N,N-Dimethylacetoacetamide	[2044-64-6]	Rats: F344/N Charles River	Gavage	Waidyanatha
Dimethylamine borane	[74-94-2]	Human skin cells Rats: Harlan Sprague Dawley	*In vitro*	Germolec
Dimethylethanolamine	[108-01-0]	Mice: B6C3F1 Rats: Wistar	Gavage	Irwin
2′,2‴-Dithiobisbenzanilide	[135-57-9]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Gavage	Sanders
Ephedrine + caffeine combination	[299-42-3] [58-08-2]	Rats: F344	Gavage	Dunnick
Furan	[110-00-9]	Rats: F344 (NCTR)	Gavage	Irwin
Furan	[110-00-9]	Rats: Tg.Lac1/C57BL/6 (Big Blue)	Gavage	Irwin
Ginkgo biloba extract	[90045-36-6]	Human liver microsomes and hepatocytes	*In vitro*	Chan
Gum guggul extract		Human liver microsomes	*In-vitro*	Wyde

Chemical	[CASRN]	Species/Strain	Route	Project Leader
2-Hydroxy-4-methoxybenzophenone	[131-57-7]	Mice: B6C3F1 Rats: Sprague Dawley	Gavage	Auerbach
Ionic liquid (1-butyl-1-methylpyrrolidinium chloride)	[479500-35-1]	Mice: B6C3F1 Rats: F344/N	Intravenous	Hooth
Ionic liquid (n-butylpyridinium chloride)	[1124-64-7]	Mice: B6C3F1 Rats: F344/N	Topical application	Hooth
Isocyanuric acid	[108-80-5]	Rats: Fischer 344	Gavage	NCTR
Isocyanuric acid	[108-80-5]	Rats: F344 (NCTR)	Intravenous	NCTR
Melamine	[108-78-1]	Rats: F344 (NCTR)	Gavage	Tolleson
Melamine cyanurate	[37640-57-6]	Rats: F344 (NCTR)	Gavage	Tolleson
Melamine + cyanuric acid combination		Rats: F344 (NCTR)	Feed	Tolleson
Melamine + cyanuric acid combination		Rats: F344 (NCTR)	Intravenous	Tolleson
2-Methoxy-4-nitroaniline	[97-52-9]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Gavage	Auerbach
L-beta-Methylaminoalanine	[15920-93-1]	Rats: Harlan SD Mice: B6C3F1	Gavage	Sanders
Fullerene C60	[99685-96-8]	Rats: F344/N	Intratracheal	Sanders
Rutile TiO_2	[1317-80-2]	Mice: SKH-1 Hairless	Topical application	NCTR
Nanoscale silver	[7440-22-4]	Rats: SD	Gavage	Walker
Nanoscale silver	[7440-22-4]	Rats: SD	Intravenous	Walker
Nanoscale silver	[7440-22-4]	Rats: SD	Gavage	Walker
Silver acetate	[563-63-3]	Rats: SD	Intravenous	Boudreau
Silver acetate	[563-63-3]	Rats: SD	Gavage	Boudreau
Triclosan	[3380-34-5]	Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Topical application	Fang
Toxicogenomics study of allylbenzene and propenylbenzene class flavor constituents • Anethole • Estragole • Eugenol • Isoeugenol • Isosafrole • Methyleugenol • Myristicin • Safrole	 [104-46-1] [140-67-0] [97-53-0] [97-54-1] [120-58-1] [93-15-2] [607-91-0] [94-59-7]	Human liver microsomes	*In vitro*	Waidyanatha

Table 28: Disposition, Metabolism and Toxicokinetic Studies Planned for FY 2011

Chemical	[CASRN]	Species/Strain	Route
Bisphenol AF	[1478-61-1]	Rats: Harlan SD Mice: B6C3F1	Gavage
2-Ethylhexyl *p*-methoxycinnamate	[5466-77-3]	Mice: B6C3F1 Rats: Harlan SD	Dermal
Tris(4-chlorophenyl)methane	[27575-78-6]	Mice: B6C3F1 Rats: Harlan SD	Intravenous
Tris(4-chlorophenyl)methanol	[3010-80-8]	Mice: B6C3F1 Rats: Harlan SD	Gavage

Genetic and Alternative Test Systems

Biomolecular Screening

In 2008, the NTP established a high throughput screening (HTS) initiative, representing a new paradigm in toxicological testing. During 2010 the NTP continued using this HTS approach to screen for mechanistic targets active within cellular pathways critical to carcinogenicity, reproductive and developmental toxicity, genotoxicity, neurotoxicity, and immunotoxicity. The NTP's HTS program is administered through the Biomolecular Screening Branch (BSB).

The goals of the HTS Program are:

- To prioritize substances for further in-depth toxicological evaluation (to judiciously allocate efforts and resources to maximize public health impact)
- To identify mechanisms of action for further investigation (e.g., disease-associated pathways)
- To develop predictive models for biological responses in humans and animals (predictive toxicology)

Much of the research conducted in support of the HTS program is coordinated with the EPA, the National Human Genome Research Institute (NHGRI), and the FDA through a Memorandum of Understanding (see page 84).

Contact Information: Dr. Raymond Tice, Chief BSB, *tice@niehs.nih.gov*. HTS website: *http://ntp.niehs.nih.gov/go/28213*

Non-mammalian models – C. elegans

The NTP is currently evaluating *Caenorhabditis elegans* (*C. elegans*) as a study organism for assessing the effects of potential developmental and neurological toxicants on multi-cellular organisms. *C. elegans* is a roundworm about 1 mm in length that lives freely in soil and feeds on bacteria. The use of *C. elegans* is consistent with NTP's strategy to reduce the number of mammals used in testing. Several toxicology assays for feeding, growth, reproduction, and movement of *C. elegans* have been developed. Table 29 lists ongoing and completed *C. elegans* studies.

Table 29: Ongoing and Completed *C. Elegans* Studies During FY 2010

Chemical	[CASRN]
3-Aminopyridine	[462-08-8]
2-Aminopyridine	[504-29-0]
4-Aminopyridine	[504-24-5]

Secondary screens using the *C. elegans* model (http://www.niehs.nih.gov/research/atniehs/labs/bmsb/index.cfm) continue to be developed; the 309 compounds used in Phase I of EPA's ToxCast™ Program were screened in *C. elegans* using a growth assay and the data compared with the results of a zebrafish embryo assay conducted by the EPA. The Tox21 partners continue to identify and use a full spectrum of secondary and tertiary screening assays to further define and characterize activities identified in initial quantitative high throughput screens (qHTS) and quantitative high content screens (qHCS).

Contact Information: Jonathan Freedman, *freedma1@niehs.nih.gov.*

Toxicogenomics Studies

The NTP is working to bring the latest toxicogenomics technology into its testing program to help revolutionize the way NTP conducts its studies. Toxicogenomics examines how the entire genetic structure, or genome, is involved in an organism's response to environmental toxicants. It applies gene and protein technologies to environmental medicine by studying the effect of toxicants on gene activity and specific proteins produced by genes. This information could be useful to identify biomarkers of disease and exposure to toxic substances and for understanding individual genetic susceptibilities.

Preliminary toxicogenomic studies suggest that gene expression often is predictive for phenotypic alterations. The NTP is interested in determining if differential gene expression (DGE) analysis can provide indicators of toxicity at earlier time points and at lower doses than is possible with traditional toxicology parameters. DGE may provide more than a genotypic link to a morphology, because it is expected to provide insights into the pathogenesis of the disease and how different rodent models respond to toxicants.

Perhaps the most exciting potential of toxicogenomics is the possibility to identify biomarkers of exposure or biomarkers of effect. Changes that can be found in easily obtainable samples (blood, urine) could then be monitored in clinical studies. When the technology is validated, it will allow repeated sampling during long-term NTP studies to determine whether chemical exposures can be detected or whether developing cancers will provide a genetic signature.

The NTP is currently evaluating study conditions that may contribute to gene expression (e.g., animal and tissue variability), best methods of tissue sampling, and establishing standards for conducting toxicogenomic studies under laboratory conditions. However, a long-term goal of the NTP is to find better and more accurate methods of predicting potential carcinogenicity, because current NTP carcinogenicity studies take four to five years to complete and are costly. Planned or ongoing NTP toxicogenomic studies are listed in Table 30.

Table 30: Toxicogenomics Studies (Planned or Ongoing) in FY 2010

Study	[CASRN]	Species/Strain	Study Route	Length	Project Leader
Aflatoxin B1	[1162-65-8]	Rats: F344/N	Feed	90 days	Irwin
Effect of the estrous cycle on hepatic transcriptome		Rats: Wistar Han	Not applicable	90 days	Irwin
Microcystin mixture	[101043-37-2] [96180-79-9]	Rats: F344/N	Intravenous	1/2/6/24 hrs	Walker
Microcystin – LR	[101043-37-2]	Rats: Wistar Han	Intravenous	1/2/6/24 hrs	Walker
Microcystin – LA	[96180-79-9]	Rats: F344/N	Intravenous	1/2/6/24 hrs	Walker
Evaluation of rat liver carcinogens and non-carcinogens administered by feed in: • Acetaminophen • Aflatoxin B1 • 1-Amino-2,4-dibromoanthraquinone • Ascorbic acid • Methyleugenol • *N*-nitrosodimethylamine • 1-Tryptophan	 [103-90-2] [1162-65-8] [81-49-2] [93-15-2] [50-81-7] [62-75-9] [73-22-3]	Rats: F344/N Tac	Feed Gavage Water	8 weeks 13 weeks	Irwin
Toxicogenomics study of allylbenzene and propenylbenzene class flavor constituents • Anethole • Estragole • Eugenol • Isoeugenol • Isosafrole • Methyleugenol • Myristicin • Safrole	 [104-46-1] [140-67-0] [97-53-0] [97-54-1] [120-58-1] [93-15-2] [607-91-0] [94-59-7]	Rats: F344/N Tac	Gavage	90 days	Irwin
Microarray analysis studies: • 2,3,4,7,8-Pentabromodibenzofuran • 1,2,3,7,8-Pentabromodibenzofuran • 2,3,7,8-Tetrabromodibenzofuran • 2,3-Dibromo-7,8-dichlorodibenzo-p-dioxin • 2,3,4,7,8-Pentachlorodibenzofuran • 1,2,3,7,8-Pentachlorodibenzofuran	[51974-40-4] [13116-92-2] [107555-93-1] [67733-57-7] [50585-40-5] [57117-31-4] [57117-41-6]				DeVito
Pentabromodiphenyl oxide (technical) (DE 71)	[32534-81-9]	Rats: Wistar Han	Gavage	Gestation day 6 - Postnatal day 21	Dunnick

Cellular and Molecular Pathology

The Cellular and Molecular Pathology Branch (CMPB) is internationally recognized as a leader in toxicologic pathology. The CMPB has developed workshops, symposia, atlases, study sets, seminars, and other educational media for use by NTP pathologists (both CMPB staff and NTP contractors) as well as the global community. The NTP often sets standards that are highly valued by regulators at EPA, FDA, and NIOSH as well as other agencies and institutes around the world.

Digital Pathology

Digital photomicroscopy and slide scanning technologies are now routinely used for NIEHS/NTP studies and have led to the ability to publish and present stellar microscopic images, and through web-based telepathology, to conduct pathology peer reviews and seek instantaneous opinions from pathologists at remote locations around the world. During the evaluation of an NTP study, pathologists identify representative lesions for photomicroscopy or slide scanning and inclusion in the new pathology database. It is estimated that 70% of the NTP studies require photography, ranging from approximately 5-20 photographs per study. Routinely, the images are used for the PWG reviews. The NTP, in partnership with NCTR, is currently evaluating the diagnostic quality of digital histopathology by directly comparing the diagnoses given for a digital image to the corresponding glass slide. To date, ten PWGs have been evaluated and reveal promising results. During the past decade the NTP has established and maintained a state-of-the-art approach to capturing and archiving digital images of rodent pathology in a database that has grown to over 60,000 images. The images are primarily obtained by light microscopy but also include electron microscopy as well as MRI and microcomputed tomography (micro-CT). New types of imaging, such as MRI and micro-CT, for both *in vivo* and *ex vivo* studies, provide significant increases in data content and efficiency and allow a more complete examination of tissues and organs from animals involved in experimental studies. The images are categorized by species, sex, organ system, treatment, and dose.

Atlas for Documenting Diagnostic Criteria for Non-neoplastic Lesions

In efforts to standardize and improve the diagnostic accuracy of non-neoplastic lesions in the NTP database, CMPB pathologists have been working to improve and revise the NTP's Pathology Code Table and nomenclature for non-neoplastic lesions of the mouse and rat. Groups of two to three pathologists are generating terminology for specific organ systems and have been gathering or generating photomicrographic images of each lesion for the atlas. Lesion thresholds and severity scoring are also being addressed. Dr. Mark Cesta is leading the effort, which has completed drafts for six organ systems thus far. Additionally, NTP pathologists are in working groups for the Society of Toxicologic Pathology's International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) project, which is developing an internationally accepted nomenclature standardization of rodent neoplastic and non-neoplastic lesions. The project is relying on NTP expertise and using the NTP's digital database of >60,000 pathology images for examples for the atlases. Approximately eight organ system chapters have been submitted for review.

Hepatobiliary Atlas of the Embryonic Mouse

Dr. Susan Elmore, Julie Foley, and Dr. Laura Crawford (a veterinary student in the Summers of Discovery program at NIEHS) published Histology atlas of the developing mouse hepatobiliary system with emphasis on embryonic days 9.5-18.5. (*Toxicol Pathol.* 2010;38(6):872-906). This atlas provides phenotyping information to better address *in utero* exposure toxicity studies, and an investigation into causes of embryonic, fetal, or perinatal deaths.

Immunotoxicology Pathology Peer Review

Because of a constant effort to improve data quality, the NTP is applying the same level of rigorous pathology peer review to its immunotoxicology studies as it has traditionally applied to its subchronic and chronic carcinogenicity bioassays. This effort has included both the development of NTP specifications and pathology training for these studies. Six studies have been completed to date and have final pathology data.

Reproductive and Developmental Toxicology Pathology Peer Review

As with the immunotoxicology studies, the NTP has decided to apply the same rigorous pathology peer review process to its reproductive and developmental toxicity studies. These multigenerational RACB studies have been redesigned to provide a more complete picture of the potential for agents to cause reproductive and developmental toxicity. An NTP reproductive and developmental toxicity study pathology specifications document has been developed.

CL Davis Foundation Independent Study Center

CMPB is designated an Independent Study Center by the CL Davis Pathology Foundation and as such serves in-house and area trainees with study materials kept either at the NIEHS or NTP Archive in Research Triangle Park, NC. The study sets have been upgraded over the years with many new CDs comprising diseases of cattle, pigs, horses, primates, cat and dog, fish, wildlife, and ophthalmic pathology. These are in addition to rodent videos and other web-based teaching materials.

RTP Rodent Pathology Courses

CMPB staff is involved in the organization and presentation of biennial Research Triangle Park Rodent Pathology Courses. These meetings are designed to showcase local pathology talent but also include international pathologists and basic and medical scientists. The September 26-28, 2010 meeting in Cary, NC was focused on hepatobiliary pathology. Drs. David Malarkey and Susan Elmore of CMPB were on the organizing committee. They and Dr. Mark Hoenerhoff and Julie Foley gave presentations.

11th Annual NTP Satellite Symposium

The 11th Annual NTP Satellite Symposium was held on June 19, 2010, in advance of the jointly sponsored 29th Society of Toxicologic Pathology (STP) and International Federation of Societies of Toxicologic Pathologists (IFSTP) Annual Meeting in Chicago, Illinois. Chaired by Dr. Susan Elmore, this symposium was one of the most highly attended interactive sessions of the meeting. The theme for the 2010 symposium was Pathology Potpourri and included presentations of unusual lesions in the liver, pancreas, preputial gland, kidney, nasal septum, retina, skin, lung, ovary, and vascular system. Also included were example definitions and discussion of proposed INHAND nomenclature for proliferative and nonproliferative entities of the central and peripheral nervous system and cardiovascular system. Drs. David Malarkey and Deepa Rao also participated.

Modified Sampling of the Nervous System in Routine NTP Studies

In the past, routine evaluation of the nervous system in short and long-term studies conducted in rodents by the NTP were limited to three histological sections of brain; in occasional circumstances, three sections of the spinal cord and a section of the sciatic nerve were also included. The increasing occurrence of human neurological diseases and subsequent cost burden on the economy, the role of unidentified environmental stressors in neurodegenerative disorders such as Parkinson's disease and autism, multiple therapeutic drug-induced neuropathies observed in human clinical trials, and the exponential increase in use of chemicals with unknown neurotoxic potential within the environment or workplace, necessitate a more extensive evaluation of the

nervous system during routine screening for toxicity and carcinogenicity of chemicals, drugs, and biological agents by the NTP. Hence, the NTP has modified its protocol toward a more comprehensive histopathological evaluation of the nervous system that will allow a more complete examination of key anatomic subsites not previously examined. It is expected that this modified approach will increase the sensitivity of detecting and achieving mechanistic understanding of neurotoxicants and neurocarcinogens important to human neurologic and neurodegenerative disorders.

Molecular Mechanisms of Chemically Induced Neoplasia

NTP studies have identified several genetic alterations in chemically induced rodent neoplasms that have potential mechanistic implications for human cancer. Identifying such genetic alterations in NTP rodent models exposed to environmental contaminants, occupational chemicals, and other compounds demonstrates the importance of these studies in evaluating potential human health risks. These studies provide convincing molecular data that serve to complement the traditional gold standard histopathology data. NTP staff has initiated several studies investigating the molecular mechanisms of tumorigenesis in NTP studies. Studies included investigation of genetic and epigenetic alterations in liver, lung, mesothelioma, and colon tumors induced by compounds in NTP studies. Protocols to further standardize frozen tissue collection from NTP chronic studies for molecular biology analysis, including gene expression and protein analysis, have been initiated. Using the high quality samples obtained from the NTP chronic studies in conjunction with high throughput global gene expression profiling, important similarities were discovered between mouse and human tumors at the molecular level. Additionally, this technology provided important information on chemical-specific events leading to tumorigenesis. It is becoming increasingly important in NTP studies to identify pre-disease early genetic and epigenetic events in the process of toxicity and carcinogenicity in order to establish predictive as well as preventative measures to minimize human health hazards. Evaluation of alterations in gene and protein expression in tissues during the pre-neoplastic stages will provide important data about the initiating events that will provide critical information on predictive events in the pathogenesis of chemically induced neoplasms in NTP studies. NTP contributors were Drs. Mark Hoenerhoff, Arun Pandiri, Stephanie Lahousse, and Robert Sills, Ms. Hue Hua Hong, and Mr. Tai-Vu Ton.

Contact Information: Cellular and Molecular Pathology Branch, Dr. Robert C. Sills, Chief, *sills@niehs.nih.gov.*

NTP Postdoctoral Training Programs

Laboratory Animal Medicine Training Program

This four-year training program, under the direction of Dr. Angela King-Herbert, includes clinical and surgical responsibilities, management of animal care facilities, participation in research projects, and laboratory animal pathology. The training program is a collaborative effort between NIEHS and the University of North Carolina at Chapel Hill. Fellows interact with laboratory animal veterinarians at NIEHS and at local area academic, industrial, and government facilities to receive didactic and hands-on training in laboratory animal medicine. Two postdoctoral fellows are currently in the program, Drs. Jacquelyn Tubbs and Dr. Coralie Zegre-Cannon. Both are scheduled to take the American College of Laboratory Animal Medicine certifying examination in June 2011.

Contact Information: Dr. Angela King-Herbert, *kingher1@niehs.nih.gov.*

Toxicological Pathology Training Program

Since formalizing a training program in toxicological pathology in 2003, Dr. David Malarkey, training coordinator, and other CMPB staff have mentored 11 post-doctoral fellows and over 30 veterinary student externs. Three post-doctoral fellows, Drs. Michael Boyle, Torrie Crabbs, and Deepa Roa, and five veterinary students participated in the program during 2010. The program is designed to introduce students to the field and career opportunities in veterinary and toxicological pathology while also providing hands-on projects often leading to abstracts and publications. Post-doctoral fellows learn rodent and toxicological pathology, participate in NTP and other DIR research projects, work to achieve accuracy of NTP pathology data by assisting the NTP pathologist on NTP studies, and continue education towards achievement of board certification by the American College of Veterinary Pathologists.

Contact Information: Dr. David Malarkey, *malarkey@niehs.nih.gov.*

Toxicology and Carcinogenesis Training Program

Trainees in this program, under the direction of Dr. Paul Foster, learn to perform all aspects of contracted toxicology studies for carcinogenic or non-carcinogenic endpoints (e.g., reproductive and developmental effects, immune system function). They learn about NTP efforts in molecular toxicology and HTS and receive training applicable to regulatory or industrial toxicology. By serving as study scientists in non-laboratory positions, they evaluate the toxicity of substances of interest to the NTP. They actively participate in designing, conducting, and evaluating studies and interact extensively with chemistry, pathology, toxicokinetics, toxicogenomics, genetics, epidemiology, statistics, and molecular biology staff. Four postdoctoral fellows are currently in the program, Drs. Minerva Mercado-Feliciano, In Ok Surh, Mamta Behl, and Sang-Hyun Kim.

Contact Information: Dr. Paul Foster, *foster2@niehs.nih.gov.*

Interagency Agreements

NIEHS/NCTR Interagency Agreement

In 1992, the FDA entered into an IAG with NIEHS. The interagency agreement (IAG) is an instrument that allows chemicals nominated to the NTP to be studied for toxicity using the unique resources and facilities at NCTR. The research conducted under the IAG allows the FDA to better assess study design input and initial data on the safety of FDA-regulated products. It has allowed continued collaborative toxicity testing on compounds of interest to the FDA and NTP and has led to investigations of mechanisms of action and assessments of toxicity for many classes of chemicals including cosmetics, endocrine-disrupting compounds, food contaminants, food cooking byproducts, dietary supplements, drugs, and anesthetics. The IAG supports the Phototoxicity Research and Testing Laboratory at the NTP Center for Phototoxicology and the Nanotechnology Core Facility at the NCTR/ Office of Regulatory Affairs. All toxicology studies conducted under the IAG are designed with input from FDA regulatory scientists, NCTR and NIEHS scientists, scientists from other agencies, and invited subject matter experts. The IAG uses resources from public funds and exceptional scientific expertise to provide the best possible assessment of product safety through toxicological studies. Table 31 lists projects completed or ongoing in FY 2010.

Table 31: NIEHS/NCTR Interagency Agreement Projects in FY 2010

Study [CASRN] [Principal Investigator]	Objective and/or Rationale
para-Nonylphenol: Evaluation of Reproductive Effects over Multiple Generations [84852-15-3] *[Delclos]*	(1) To determine the effects of *p*-nonyphenol, an intermediate in the production of surfactants and other industrial products, on reproduction and on the development of reproductive and other hormone-sensitive organs when administered to CD rats over five generations; (2) to determine if subtle effects observed in the dose-range-finding study are magnified through multiple generations; and (3) to evaluate the reversibility of any observed effects.
Perinatal Carcinogenicity of Drug Combinations Used to Prevent Mother-to-Child Transmissions of HIV [30616-87-1], [134678-17-4] *[Beland]*	To determine the carcinogenicity, genotoxicity, and metabolism of antiretroviral drug combinations administered to mice transplacentally, perinatally, or neonatally. The studies include 14-day range-finding as well as 2-year chronic studies in both groups.
Effect of Topically Applied Skin Creams Containing Retinyl Palmitate on the Photocarcinogenicity of Simulated Solar Light in SKH-1 Mice [79-81-2] *[Boudreau]*	(1) To determine if retinyl palmitate applied to the skin of SKH-1 hairless mice alters the incidence of tumors produced by simulated solar and/or UV light, and (2) to determine the mechanisms of tumor promotion by retinyl palmitate.
Bioassays in the F-344 Rat and B6C3F1 Mouse Administered *Aloe vera* Plant Constituents in Drinking Water [8001-97-6] *[Boudreau]*	(1) To use 14-day studies determine dose ranges for future toxicology studies, (2) to use 90-day studies to determine the toxic effects and highest tolerated doses of the different *Aloe vera* components, including the gel and whole leaf extracts [filtered and non-filtered], and (3) to use 2-year chronic studies to determine the chronic toxicity and carcinogenic potential of Aloe vera whole leaf exctract in the rat and mouse by oral exposure administered in the drinking water.
Toxicity Studies of a Combination of AIDS Drugs in p53 (+/-) Transgenic Mice [30616-87-1; 134678-17-4] *[Leakey]*	To evaluate the potential toxicity and carcinogenicity of perinatal and chronic exposures to the AIDS drugs AZT and 3TC in C3B6F1trp53(+/-) haplodeficient F1 transgenic mice. The study includes both a range-finding and a 6-9-month chronic phase.
Genotoxicity and Carcinogenicity of Acrylamide and Its Metabolite Glycidamide in Rodents [79-06-1; 5694-00-8] *[Beland]*	To compare the carcinogenicity of acrylamide and its metabolite glycidamide in B6C3F1 mice and F344 rats treated chronically for two years.
Developmental Neurotoxicity Assessment of Acrylamide in Rats: Long-term Studies [79-06-01] [*Paule*]	To determine the consequences of long-term exposure to acrylamide on a variety of developmental milestones and measures of nervous system integrity throughout life.

Study [CASRN] [Principal Investigator]	Objective and/or Rationale
Genotoxicity and Carcinogenicity of Acrylamide and its Metabolite Glycidamide in Rodents — Range-finding/Subchronic/2-year Chronic Carcinogenicity Studies [79-06-1; 5694-00-8] [*Beland*]	To complete 13-week studies, 90-day studies, and 2-year bioassays for acrylamide and glycidamide.
Subchronic Toxicity Studies of Chondroitin Sulfate and Glucosamine Combinations in Fischer 344 and Diabetic Goto-Kakizaki Rats [3416-24-8, 9007-28-7] *[Leakey]*	(1) To investigate the potential toxicity of chondroitin sulfate and glucosamine, administered by oral gavage in male rats, and (2) to determine whether subchronic exposure of glucosamine or chondroitin sulfate potentiates the pathological effects of noninsulin-dependent diabetes in obese diabetic rats.
Toxicity Studies of Glucosamine and Glucosamine/Chondroitin Sulfate Combinations in Obese and Lean Zucker Rats [3416-24-8; 9007-28-7] *[Leakey]*	To investigate the potential toxicity of glucosamine and glucosamine/chondroitin sulfate combinations, administered by oral gavage in male rats.
DEHP Toxicokinetics in Neonatal Male Rhesus Monkeys after Intravenous and Oral Dosing [117-81-7] *[Delclos]*	(1) To quantify the metabolism and disposition of multiple, single intravenous doses of DEHP administered to male rhesus monkeys during the first 12 postnatal weeks, (2) to quantify the metabolism and disposition of multiple, single oral doses of DEHP administered to male rhesus monkeys during the first 12 postnatal weeks, (3) to use the results of this work to evaluate the feasibility and utility of a subchronic toxicity study of DEHP, and (4) to utilize blood and testicular tissue from the infant monkeys to establish methods to be utilized in the subchronic study and/or estimate variability in the endpoints to aid in determining the number of animals that will be required in each dose group for a subchronic study.
The Immunogenicity of Permanent Makeup Inks and Their Components *[Howard]*	To investigate the possibility of immunostimulation by a select group of permanent makeup inks that were associated with adverse event reports to the FDA.
Effects of Sedatives on the Metabolism of DEHP Administered by Intravenous Injection and the Relationship of DEHP Metabolism to Biological Effects in Neonatal Rats [117-81-7] *[Delclos]*	(1) To determine if the metabolic profile of DEHP is affected by sedatives potentially useful for intravenous injection studies of DEHP in neonatal rhesus monkeys and/or in common use in neonatal intensive care units and (2) to examine DEHP metabolism in neonatal rodents dosed intravenously and orally and relate this metabolism to biological effects.
Maintenance of the Transgenic p16/p19(-/-) Haplodeficient [NCTR strain code 7V] Breeding Colony *[Leakey]*	To maintain the NCTR p16/p19 breeding colony for the development of a strain of haplodeficient mice that could be used in GMM 9-month studies for rapid drug evaluation for carcinogenesis.
Determination of Carcinogenic Mechanisms for Furan in Male Fischer 344 Rats [110-00-9] *[Doerge]*	To determine the pharmacokinetic mechanisms, mutagenesis, and hepatotoxicity of low doses of the carcinogen furan in rodents.
Subchronic Studies of Usnic Acid in Fischer 344 Rats and B6C3F1 Mice [125-56-2] *[Leakey]*	To evaluate the subchronic toxicity of usnic acid in male and female Fischer 344 rats and B6C3F1 mice.
Subchronic Studies of Usnea Lichen in Fischer 344 Rats and B6C3F1 Mice [84696-53-7] *[Leakey]*	To evaluate the subchronic hepatotoxicity of *Usnea* lichen in male and female Fischer 344 rats and B6C3F mice.
Physiological Effects of Bitter Orange in Rats [94-07-5] *[Hansen]*	To determine potential physiological effects of synthetic synephrine as well as an extract from the botanical *Citrus aurantium* alone and combined with caffeine in rats with and without exercise.
Developmental Toxicity of Bitter Orange in Rats [94-07-5] *[Hansen]*	To determine potential developmental toxicity of synthetic synephrine and *Citrus aurantium* extract in rats.
Determine Potential Developmental Toxicity of Synthetic Synephrine and Citrus aurantium Extract in Rats [CAS 94-07-5] [*Hansen*]	To determine the potential developmental toxicity of synthetic synephrine, *Citrus aurantium,* and possible potentiation of the toxicity by caffeine.
Mechanisms of Nevirapine Carcinogenicity [129618-40-2] *[Beland]*	To determine the mechanism by which nevirapine induces liver tumors in rats.

Study [CASRN] [Principal Investigator]	Objective and/or Rationale
A Toxicological Evaluation of Nanoscale Silver Particles in Rodents [7440-22-4] *[Boudreau]*	(1) To determine if reducing the size of silver particles to nanoscale changes the absorption, biodistribution, and excretion as well as the toxicity, and (2) to determine the effects of reducing the particle size to nanoscale of a compound that has been regarded as nontoxic in micron and above sizes.
Evaluation of the Toxicity of Bisphenol A (BPA) in Male and Female Sprague Dawley Rats Exposed Orally from Gestation Day 6 through Postnatal Day 90 [80-05-7] *[Delclos]*	(1) To assess the toxicity of BPA in perinatally dosed rats study, and (2) to evaluate estrogenic endpoints from the F1 generation dosed perinatally with BPA, via gavage.
Two-Year Carcinogenicity Bioassay of Furan in F344 Rats [110-00-9] [Beland]	To determine the dose-response relationship for the carcinogenicity of furan in F344 rats.
The Role of Perinatal Development on Toxicokinetics of BPA [80-05-7] *[Doerge]*	To develop additional data from rat and monkey exposures that will be used in the creation and validation of a PBPK model to predict internal exposures to free BPA in the appropriate target tissues of fetuses and babies that are derived from food contact and medical device exposures.
Assessment of the Nephrotoxic Effect of a Combined Exposure to Melamine and Cyanuric Acid [108-78-1; 64-18-6] *[Gamboa Da Costa]*	To investigate the toxic effects noted in cats and small children who were exposed to melamine and cyanuric acid via adulterated food supplies. The toxicity was noted in the kidneys of the pets and children. The study will include a 28-day NOAEL study.
Neurotoxicity Assessment of Cell Phone Radiofrequency Radiation (RFR) using Rat and Bovine Brain Microvascular Endothelial Cells as Model Blood Brain Barrier Systems, PC-12 Cultured Cells, and Whole Animal Models (mice and rats) [*Ali*]	(1) To determine whether power levels of RFR that are emitted from mobile phones produce any changes in the CNS of mice and rats, and (2) to determine if there are disruptions in the blood brain barrier after being subjected to RFR radiation.
Range-finding, Mechanistic and Toxicokinetic Studies of Usnic Acid and Usnea barbata Herb in Fischer 344 Rats and B6C3F1 Mice [125-46-2, 84696-53] *[Leakey*]	To complete a standard 14-day range-finding study with both compounds administered in feed.
Vehicle Selection for Triclosan Dermal Toxicity Studies in B6C3F1 Mice [3380-34-5] [*Fang*]	To determine ADME toxicokinetics after an appropriate solvent is determined for dermal application.

Contact Information: Dr. Paul Howard, *paul.howard@fda.hhs.gov* and Dr. Nigel Walker, *walker3@niehs.nih.gov*.

NIEHS/NIOSH Interagency Agreement – Comprehensive Assessment of Occupationally-Relevant Exposures

The NTP is coordinating an effort with NIOSH to better understand worker exposures, identify occupational health research gaps, and educate workers. Current efforts listed in Table 32 address worker exposures to welding fumes, nano-sized materials, food flavorings, and indium compounds.

Table 32: NIEHS/NIOSH Interagency Agreement on Occupationally Relevant Exposures

Study [Principal Investigator]	Objective and/or Rationale
Administrative Support *[Toraason]*	To enable NIOSH scientists to (1) participate in review and oversight of NTP activities and (2) attend NTP-related meetings in Research Triangle Park, NC and Washington, DC.
Assess the Feasibility of an Occupational Exposure Assessment of Welding Fumes with Emphasis on Manganese Compounds *[Hanley]*	(1) To identify industries (e.g., construction, shipbuilding, railroad, and manufacturing), companies, and/or unions involved in welding operations where the potential for substantial manganese exposure exists for exposure assessments; (2) to develop methods to identify specific manganese compounds, different valence states, and potential solubility contained within various welding fumes matrices; and (3) to characterize welding fume exposures based on welding-associated jobs, tasks, and processes.
Exposure Assessment of Diacetyl and Other Flavorings in Food Production Industries *[Curwin]*	(1) To characterize workplace inhalation exposures to diacetyl in food production industries that use food flavorings, (2) to document high-exposure activities and processes in flavored food production industries, (3) to identify work practices and procedures that affect exposure, (4) to document engineering controls, and (5) to field test novel techniques for both gravimetric and volatile sampling.
Exposure Assessment of Dithiobisbenzanilide (DTBBA) in a Manufacturing Setting *[Wurzelbacher]*	(1) To identify worker populations at increased risk of inhalation and surface exposure to DTBBA during a manufacturing process, (2) to develop a NIOSH analytical method for quantitatively assessing DTBBA airborne particulate and surface exposures, and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to DTBBA.
Assessment of Use of Indium and Indium Compounds in the Workplace *[Hines]*	(1) To contact and visit companies to determine indium materials being used, jobs and processes with potential indium exposure, exposure controls, and indium use trends; (2) to attend the Semiconductor Environmental Safety and Health Association meeting to establish contacts in industry and other organizations involved in indium-related applications; and (3) to conduct preliminary sampling for indium, if possible.
Exposure Assessment of Engineered Nanoparticles *[Geraci]*	(1) To identify workplaces engaged in the synthesis, manufacture, and use of engineered nanomaterials, and (2) to characterize workplace exposure to selected engineered nanoparticles.
Exposure Assessment of 1-Chloro-4-(trifluoromethyl) benzene (PCBTF) *[Harper]*	(1) To identify worker populations at elevated risk of inhalation and surface exposure to PCBTF during manufacturing processes, (2) to update a previously published analytical method for quantitatively assessing PCBTF airborne vapors and surface exposures to allow the use of capillary column chromatography, and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to PCBTF.
Cardiovascular Toxicity Assessment of Subchronic Inhalation Exposure to Fullerene C60 *[Erdely]*	(1) To evaluate potential cardiovascular toxicity of fullerene C60 in animal models using molecular and biochemical analysis of cardiovascular tissue and blood samples from NTP inhalation studies, and (2) to correlate the findings with the results from histopathology, particle distribution, and blood chemistry studies.

Contact Information: Dr. Dori Germolec, *germolec@niehs.nih.gov* and Dr. Mark Toraason, *mht1@cdc.gov*.

NIEHS/NIOSH Interagency Agreement – Immunotoxicology

The goal of this IAG is to provide support of NTP hazard identification activities aimed at preventing diseases or adverse effects caused by environmental exposure to chemical or physical agents. These cooperative studies continue to improve risk assessment by measuring what constitutes an adverse health effect on the immune system in humans. The studies, listed in Table 33, evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases, including asthma, contact dermatitis, allergy to mold spores, chronic beryllium disease, allergic rhinitis, and silicosis. These cohorts are being studied for a number of endpoints including impact of genetic polymorphisms on development of inflammatory disease and clinical outcomes, and identification of unique immunological biomarkers for disease. The NIOSH Laboratory for Occupational Genomics serves as a resource for obtaining samples from individuals with occupational and occupationally related diseases.

Table 33: NIEHS/NIOSH Interagency Agreement on Immunotoxicology Studies, FY 2010

Study [Principal Investigator]	Objective and/or Rationale
Chronic Sinusitis and Mold Exposure *[Beezhold]*	To investigate the role of fungi in chronic sinusitis and to determine if the prevalence of fungal sensitization is different to other seasonal allergens in chronic rhinosinusitis patients. To date, the chronic rhinosinusitis and control patients have been recruited and tested. The dataset has been collected, statistically analyzed, and a manuscript is currently being prepared.
Heading off Environmental Asthma in Louisiana *[Beezhold]*	To evaluate the effectiveness of a novel asthma case management intervention among children with asthma after Hurricane Katrina in New Orleans and to assess total immunoglobulin E (IgE) and mold-specific IgE in asthmatic children before and after intervention. This project is completed. All sera have been screened and the dataset has been statistically analyzed.
NIEHS Agricultural Pesticide Study *[Beezhold]*	To evaluate allergic sensitization in a cohort of 677 farmers with or without pesticide exposures. To date, 677 farmers have been recruited and the serum total IgE and specific IgE quantified using Phadia ImmunoCap. Serum concentrations of the fungal mycotoxin deoxynivalenol have also been quantified. Currently, a manuscript is being prepared by NIOSH and NIEHS collaborators. The second phase of the study is about to begin and will evaluate allergic sensitization in a cohort of >2000 farmers located in Iowa and North Carolina.
A marker for *Aspergillus terreus* exposure *[Beezhold]*	To develop new and improved methods for detecting fungal exposure. In this project the emerging opportunistic fungal pathogen *A. terreus* has been used as a model fungal species. Terrelysin, a cytolysin and potential biomarker of fungal infection, was characterized and a recombinant protein produced. The recombinant terrelysin was then used to immunize mice to produce terrelysin specific monoclonal antibodies (mAbs). Seven specific mAbs were produced and used to characterize the production of terrelysin. mAb binding sites are currently being determined in epitope mapping experiments. NIOSH anticipates the development of a sensitive immunoassay that may be used in the serological detection of this biomarker.
Animal model for airway exposure to dry fungal aerosols *[Beezhold]*	To develop a murine model of dry fungal exposure to better mimic natural human exposures to fungi. In collaboration with aerosol scientists at NIOSH, an acoustical generation system has been developed. In preliminary experiments, histopathology and bronchoalveolar lavage fluid analysis demonstrated pulmonary deposition of conidia following dry fungal bioaerosol exposure. Future experiments are planned to further characterize the exposures and to characterize the immune responses associated with various fungal species that frequently colonize water-damaged buildings or are occupationally relevant.
The Role of Genetic Variation in Environmental and Occupational Diseases - ICD *[Yucesoy]*	(1) To investigate whether the 24-hour irritant patch test is predictive of occupational hand dermatitis caused by high exposure to hand washing in health care workers, and (2) to investigate association between genetic variations in specific candidate genes (with emphasis on variants of cytokines, MHC region, antioxidant enzyme genes and genes related to skin barrier integrity) and irritation threshold levels of the subjects with development of ICD. This study is in collaboration with Case Western Reserve University and West Virginia University.

Study [Principal Investigator]	Objective and/or Rationale
The Role of Genetic Variation in Environmental and Occupational Diseases - Allergic Contact Dermatitis (ACD) *[Yucesoy]*	(1) To investigate genetic factors in individuals predisposed to develop ACD, specifically induced by nickel and (2) to investigate genetic factors involved in the development of ACD in individuals sensitized to weak allergens, individuals sensitized to allergens that require metabolism in the skin, and individuals who react to more than three allergens of the standard screening series. This study is in collaboration with Case Western Reserve University and Dartmouth-Hitchcock Medical Center.
Role of Genetic Variation in Environmental and Occupational Diseases – Occupational Asthma *[Yucesoy]*	(1) To investigate whether genetic variations in specific candidate genes (e.g., cytokine, MHC region, antioxidant enzyme genes) are associated with asthma induced by diisocyanates, and (2) to investigate potential associations between genetic variations in candidate genes and occupational asthma caused by low molecular weight agents. This project is in collaboration with the University of Montreal and the University of Cincinnati.
The Role of Genetic Variation in Environmental and Occupational Diseases – Chronic Beryllium Disease (CBD) – *[Yucesoy]*	To investigate the contribution of genetic variations in the MHC region to the development of beryllium sensitization and CBD. This study is in collaboration with National Jewish Medical and Research Center.
Investigations into Health Effects Caused by Exposure to Indoor Air Reaction Products (supportive animal studies) *[Wells, Anderson]*	(1) To identify and measure the reaction products of gas-phase compounds present in the indoor environment, especially oxygenated organics. (2) to further develop and validate a novel *in vitro* exposure method utilizing realistic indoor chemistry scenarios to expose cells and tissues to these indoor air reaction products, (3) to complete both *in vitro* and *in vivo* assays to assess adverse health effects caused by indoor air reaction products, and (4) to further investigate the role of structurally similar indoor air chemicals present in mixtures in the indoor environment.
Toluene Diisocyanate (TDI) Monoclonal Antibody Production and Characterization (improved methods) *[Siegel]*	(1) To produce and characterize 35 monoclonal antibodies against 2,4-TDI protein and 13 monoclonal antibodies against 2,6-TDI-protein; (2) to complete characterization of all monoclonal antibodies, especially with respect to minimal epitope required for reactivity of the monoclonal antibodies to a TDI-reacted chemical; and (3) to examine the utility of select monoclonal antibodies for immunoassay, immunohistochemistry, and proteomic analyses of tissues after TDI exposure.
Immunological Mechanisms of Occupational Rhinitis Induced by Diisocyanate Exposure (supportive animal studies and field studies) *[Johnson]*	(1) To use specific inhalation challenge with suspected diisocyanates to diagnose allergic rhinitis in workers from Canada and Spain who are exposed to diisocyanates and then clinically phenotyped for upper and lower airway disease, (2) to collect nasal mucosal samples from workers with diisocyanate rhinitis and use whole genome approaches to study mechanisms of disease, (3) to identify molecular targets in the human nasal mucosa for biomarker development and validation using the NIOSH TDI rhinitis mouse model, and (4) to develop the mucosal sampling technique and identified biomarker(s) into a simple and non-invasive tool for worker health surveillance and early diagnosis of sensitization/disease.
Assessing Exposures to Asthmagenic Cleaning and Disinfecting Products Among Healthcare Workers *[Virji]*	(1) To investigate the use of cleaning and disinfectant products which have been identified as an important risk factor for asthma in healthcare workers; (2) to identify and quantify exposures to cleaning and disinfectant product-associated asthmagens or their surrogates in six healthcare occupations; (3) to characterize job-tasks and activities, work practices and workplace factors and evaluate their impact on exposure levels; (4) to develop exposure assessment survey instruments and questionnaires; and (5) to revise an existing asthma-specific JEM for an epidemiologic study of asthma in healthcare. Exposure assessment for selected VOCs was conducted in two Veterans Administration health care facilities in 2010. This work will ultimately lead to identification of those agents most associated with asthma in the healthcare environment, enabling prioritization for detailed immunotoxicological evaluation as well as preventive intervention studies.
Determination of Total IgE, Antinuclear Antibodies and Atopy In Plasma From Members of Upper Midwest Health Study, A Case-Control Study of Intracranial Gliomas (field study) *[Biagini]*	To assess members of the Upper Midwest Health Study (1) to determine total IgE, antinuclear antibodies, and atopy in plasma, and (2) to test for common allergies.
Antibody Levels in Systemic Lupus Erythematosus (field study) *[Biagini]*	To measure total serum IgA, IgM and IgG in sera from systemic lupus erythematosus patients to investigate whether adjustment for total immunoglobulin levels may unmask differences in serum IgE levels.

Contact Information: Dr. Dori Germolec, *germolec@niehs.nih.gov* and Dr. Mark Toraason, *mht1@cdc.gov*.

NTP/NHGRI/EPA Interagency Agreement – High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings

A five-year Memorandum of Understanding (MOU), High Throughput Screening, Toxicity Pathway Profiling and Biological Interpretation of Findings, was signed on February 14, 2008. With this MOU, NTP partnered with the NHGRI's NIH Chemical Genomics Center (NCGC) and the U.S. EPA's National Center for Computational Toxicology located within the Office of Research and Development. A central component of this MOU is exploration of qHTS and tests using phylogenetically lower animal species (e.g., fish, worms), as well as high–throughput, whole-genome analytical methods to evaluate mechanisms of toxicity. Ultimately, the data generated by these new tools will be provided to risk assessors to use to protect human health and the environment. On July 19, 2010, an amended five-year MOU was announced that was signed by the original three partners plus the U.S. Food and Drug Administration (FDA). The FDA brings to the partnership experience in human diseases, animal models of human disease, and expertise in toxicity pathway analysis and computational toxicology. Their active participation is in recognition of the FDA's commitment to developing new methods to evaluate the toxicity of the substances they regulate.

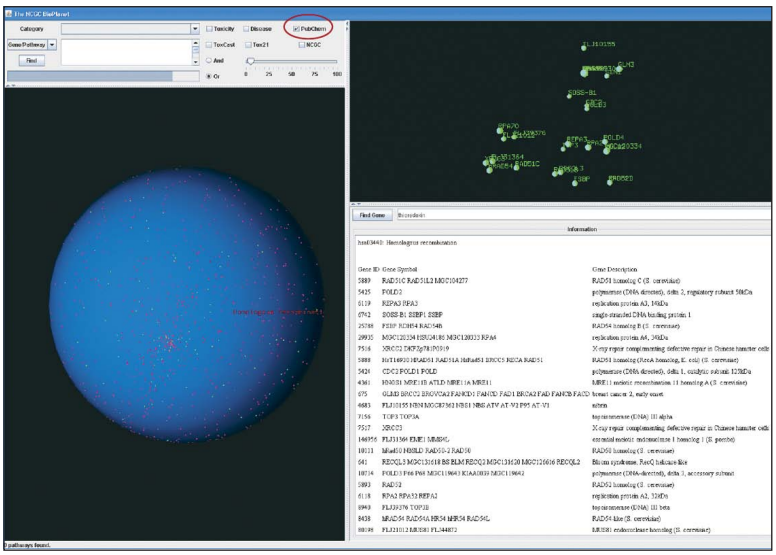
The goals of this MOU are to investigate the use of these new tools to (1) identify mechanisms of chemically induced biological activity, (2) prioritize chemicals for more extensive toxicological evaluation, and (3) develop more predictive models of *in vivo* biological response. The results should yield test methods for toxicity testing that are more scientifically and economically efficient and models for risk assessment that are more biologically based. This should reduce or replace animals in regulatory testing and is anticipated to occur in parallel with an increase in our ability to evaluate the large numbers of chemicals that currently lack adequate toxicological evaluation. Through this partnership, it is possible to pool resources, overcome the resource limitations of a single agency, build on existing expertise, and avoid the need to create a new administrative and support structure.

By the end of FY 2010, a library of approximately 2,800 compounds provided to the NCGC for qHTS by NTP and EPA had been tested in approximately 100 different assays. These assays broadly evaluated the ability of compounds (1) to induce, in various cell lines, cytotoxicity, apoptosis, DNA damage, changes in methylation status, mitochondrial toxicity, and various stress response pathways (e.g., antioxidant, hypoxia, heat shock), or (2) to act as an agonist or antagonist in 12 different nuclear receptors including the estrogen and androgen receptors. Included among these studies were those to evaluate differential sensitivity among cells from humans by exposing ~80 CEPH panel HapMap cell lines to 240 toxic chemicals and evaluating the extent of cytotoxicity and caspase 3/7 induced by each chemical .

During FY 2010, the partners continued to work on establishing a library of ~10,000 compounds that broadly characterizes and defines the chemical-biological space occupied by chemicals of toxicological concern. This library, to be completed by mid-2011, will be tested at the NCGC with qHTS and qHCS that provide information on critical cellular pathways. Chemical analysis studies to determine the identity, purity, and stability of all compounds in this library were initiated and will continue through FY2011. Starting in FY2011, this library will be screened in triplicate against a battery of nuclear receptor and stress response pathway assays at the NCGC. Testing was started of a subset of these compounds (~700) in Phase II of EPA's ToxCast™ Program (*http://www.epa.gov/ncct/toxcast/*). The data from these assays, along with full chemical characterization and assay protocol details, are being deposited into publicly accessible, relational databases such as the National Library of Medicine's PubChem (*http://pubchem.ncbi.nlm.nih.gov/*), EPA's ACToR (*http://www.epa.gov/ACToR/*) and NTP's CEBS (*http://www.niehs.nih.gov/research/resources/databases/cebs/*).

In FY 2011, the MOU will also evaluate the differential sensitivity of cells from humans by screening >1000 densely sequenced lymphoblastoid cell lines against 180 toxic chemicals and evaluating the resulting extent of cytotoxicity. To conduct the level of screening planned for FY 2011 and in subsequent years, the NCGC purchased a new robot in FY 2010 with operation scheduled for March 2011.

The NCGC BioPlanet



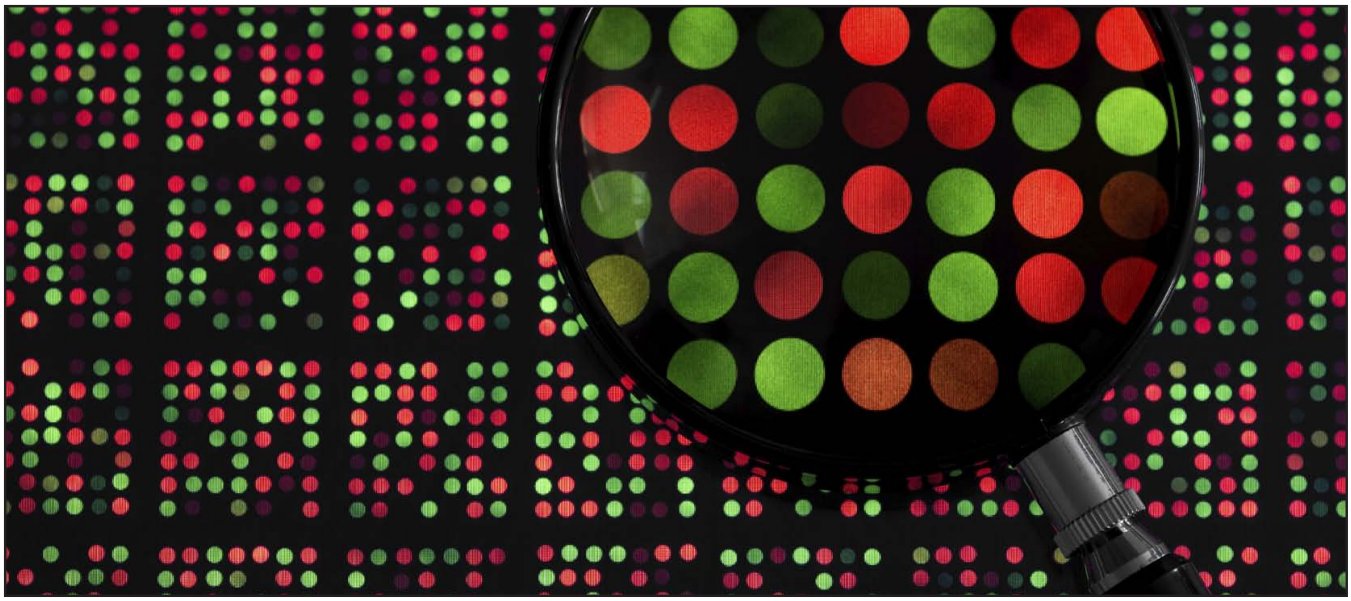
No one comprehensive and uniform resource covers all known annotations of pathways and no single platform allows integrated browsing, retrieval, and analysis of information from the many existing individual pathway resources; therefore, the NCGC (with support from the NTP) built an integrated pathway resource that hosts information on ~1100 human pathways from manually curated and publicly available resources. The NCGC BioPlanet complements this pathway warehouse by allowing easy browsing, visualization, and analysis of the universe of pathways. The main view of the BioPlanet shows the mapping of all known human pathways on a 3D globe, where each spot represents a pathway. Selecting a pathway on the globe will place all components of the selected pathway in the detailed view window. Detailed descriptions of all genes in the selected pathway are shown below the 3D graphics. When multiple pathways are selected at the same time, the view shows all unique gene components within selected pathways. Since the coordinates of genes are generated globally and are not tied to any specific pathway, this allows the visualization of multiple, predefined pathways as one extended pathway that better shows the interaction between different biological processes. The BioPlanet is searchable by any gene or pathway identifier, and also by disease relevance (prevalence of disease genes), toxicity relevance (occurrence of genes in toxicology literature), and availability of probing assays in PubChem.

NTP Archives

NTP archival tissues represent a significant and underutilized resource, so in FY 2010 NTP initiated pilot studies to evaluate the extent to which gene expression signatures can be reliably derived from the molecular analysis of tissue samples collected from the laboratory animals used in NTP's toxicological studies and stored as formalin- fixed, paraffin-embedded (FFPE) tissues in the NTP archives. Signature expression profiles are critical sets of altered transcripts or proteins that distinguish toxicity and disease from a comparable normal state. Development of such signatures would further our understanding of pathological changes, mechanisms, and critical pathways in agent-induced toxicity. Further, such signatures could contribute to the identification of useful targets for *in vitro* assays, to an evaluation of the correlation between *in vitro* test results and *in vivo* toxicological outcomes, and to the development of predictive models of toxicity.

DrugMatrix®

Related to the goal of developing analysis tools and approaches to allow an integrated assessment of HTS endpoints and associations with findings from traditional toxicology and cancer models, the NTP acquired DrugMatrix, a toxicogenomics reference database, the accompanying extensive frozen tissue archives, and the informatics system. The NTP acquired this resource to expand the ability to develop predictive models for toxicological effects based on gene signatures, to provide additional tools for linking *in vitro* data to *in vivo* gene signatures and disease outcomes, and to provide additional tissue samples for NextGen-based investigations. It is anticipated this database will be made publicly accessible to the international scientific community through CEBS.



Mouse Methylome Project

An individual's response to exposure-related toxicity and concomitant disease is influenced at the genome level by genetic, epigenetic, gene-gene interactions (intrinsic factors) and interaction with the environment (extrinsic factors). Individual DNA sequence variation does not account for all of the heritability for susceptibility to toxicity and diseases such as asthma, cancer, diabetes, etc. An intrinsic factor that quantitative and molecular geneticists believe is the basis for the observed "missing heritability" is the methylome, an individual's genome-wide methylated CpG sequence pattern. The methylome (a component of the epigenome) may be the major epigenetic modifier of susceptibility to cancer and other chemical exposure-related diseases. Presently, there is no mouse reference database for the methylome. The DNA sequence data has significantly increased our knowledge of the genomic structure of the inbred mouse and provided the basis for imputation of the haplotype structure of more than 90 inbred strains used in biological research. The absence of a methylome reference database for the mouse significantly handicaps understanding of the mouse model in toxicology and environmentally related diseases and designing and conducting hypothesis based genetic and epigenetic research studies to understand the associated mechanisms. Two high content technologies have recently been developed that (1) determine genome-wide methylated CpG sites by deep sequencing of bisulfite treated genomic DNA to determine sequence context and cytosine methylation variation (BIS-Seq) and RNA (RNA-Seq) and (2) fractionate DNA sequences using differential restriction and/or affinity capture (MMDE-seq) to enrich for methylated DNA sequences. Together, these tools allow targeted interrogation of CpG regions of interest using bioinformatic data mining tools. These technologies will allow creation of a definitive map of the mouse liver methylome from the two parental strains (C57BL/6N and C3H/HeN) and their F1 hybrid (B6C3F1/N) offspring that exhibit dramatically different rates of interstrain and sex-dependent spontaneous liver cancers.

Contact Information: Dr. Raymond Tice, BSB Chief, *tice@niehs.nih.gov.* HTS website: *http://ntp.niehs.nih.gov/go/28213*

NIEHS/EPA Interagency Agreement – The Phthalate Initiative

Di(2-ethyl)hexyl phthalate (DEHP) and other phthalates have been nominated to the NTP for testing. To address these nominations, the NIEHS and EPA signed *The Phthalate Initiative* IAG in June 2008, which was renewed in July 2009 and 2010. Many aspects of this IAG fall under nominations previously approved by the BSC for the study of peroxisome proliferators (begun in the 1990s), the nomination of DEHP by the FDA in 2004, and the critical data need highlighted in the NTP Monograph on DEHP issued in 2006.

These studies will clarify how the peroxisome proliferator-activated receptor alpha (PPARα) develops in the rat and its relationship to DEHP-related cancer and other developmental toxicities. The studies will also provide critical data for future mixture studies using various models to inform on potential risks for toxicity over time and during development. Recent data have indicated that because phthalate esters have similar modes of action *in utero*, they show dose-addition when administered in combination; therefore, it would be appropriate to consider cumulative risk for the class, since human subjects (including fetuses) are typically exposed to multiple phthalates.

The initiative has two specific aims:

(1) Undertake an ontogeny study of PPARα in the rat to determine when the receptor is first expressed in target tissues. This study will test the hypothesis that PPARα is developmentally regulated in the rat and unlikely to contribute to toxicity initiated *in utero* after exposure to DEHP.

(2) Undertake perinatal phthalate mixture studies. These studies will test the hypothesis that exposures to mixtures of phthalates, based on their individual potencies, would result in dose-addition for cancer (and potentially other) outcomes.

Based on data generated in 2010, using a specific short-term *in utero* screen developed in the initiative to evaluate individual phthalates and mixtures in the Harlan SD rat, data have been developed for approximately 11 different phthalates and derivatives. This model is also appropriate for studying developmental effects of various phthalates. Phthalates' ability to alter fetal testicular testosterone production, induce changes in specific fetal testicular genes (especially related to steroidogenesis and testicular descent), and induce specific male reproductive tract malformations has been termed the "phthalate syndrome."

Thus far, data indicating a positive response has been obtained from butylbenzyl, di-n-butyl, di-iso-butyl, di-ethylhexyl, di-pentyl di-n-hexyl, di-iso heptyl, di-n-heptyl and di-cyclohexyl phthalate and three different preparations of di-iso-nonyl phthalate (a complex mixture). Brominated DEHP, diethyl phthalate, and di-octyl terephthalate were all negative in this fetal phthalate screen. Specific potency factors have been developed based on this screening information.

These data should guide selection of individual studies to investigate potential short-term biomarkers for toxicity, which in turn should support future perinatal bioassays and phthalate mixture work. The NTP has now designed both perinatal and standard bioassays to evaluate developmental and cancer potential from different exposure paradigms for DEHP, which should begin in early 2011. This information will be extremely valuable in assessing potential cumulative risk of phthalates, as has been advocated by a recent National Academy of Sciences committee report and efforts by EPA's Integrated Risk Information System (IRIS) program.

In the ontogeny study, the NTP is evaluating the potential role of activation of PPAR pathways in the disruption of male sexual differentiation and testis development using custom-designed PCR plates. These plates allow the determination of relative mRNA expression of PPARά, PPARδ, and PPARγ and several genes activated by PPARά including CYP4a1 on a single sample simultaneously. For six positive phthalates examined so far, none of the PPAR genes, CYP4a1, or any other genes "downstream" of PPARά are activated by any of the phthalates at a single high dosage level.

Contact Information: Dr. Paul Foster, *foster2@niehs.nih.gov*

Appendix I

NTP staff are listed alphabetically by agency

NCTR/NTP

Beland, Frederick	(870) 543-7205	frederick.beland@fda.hhs.gov
Boudreau, Mary	(870) 543-7526	mary.boudreau@fda.hhs.gov
Brakebill, Nancy	(870) 543-7785	nancy.brakebill@fda.hhs.gov
Chidambaram, Mani	(870) 543-7368	mani.chidambaram@fda.hhs.gov
Churchwell, Mona	(870) 543-7698	mona.churchwell@fda.hhs.gov
Corlett, Angela	(870) 543-7403	angela.corlett@fda.hhs.gov
Couch, Letha	(870) 543-7137	letha.couch@fda.hhs.gov
Cozart, Christy	(870) 543-7602	christy.cozart@fda.hhs.gov
Delclos, Barry	(870) 543-7372	barry.delclos@fda.hhs.gov
Doerge, Daniel	(870) 543-7943	daniel.doerge@fda.hhs.gov
Duffy, Peter	(870) 543-7054	peter.duffy@fda.hhs.gov
Fang, Jia-Long	(870) 543-7612	jia-long.fang@fda.hhs.gov
Felton, Robert	(870) 543-7504	robert.felton@fda.hhs.gov
Ferguson, Sherry	(870) 543-7589	sherry.ferguson@fda.hhs.gov
Fisher, Jeffrey	(870) 543-7703	jeffrey.fisher@fda.hhs.gov
Gamboa, Goncalo	(870) 543-7400	goncalo.gamboa@fda.hhs.gov
George, Nysia	(870) 543-7047	nysia.george@fda.hhs.gov
Guo, Lei	(870) 543-7048	lei.guo@fda.hhs.gov
Hansen, Deborah	(870) 543-7480	deborah.hansen@fda.hhs.gov
Heflich, Robert	(870) 543-7493	robert.heflich@fda.hhs.gov
Heinze, Thomas	(870) 543-7468	thomas.henize@fda.hhs.gov
Howard, Paul C.	(870) 543-7672	paul.howard@fda.hhs.gov
Law, Charles	(870) 543-7013	charles.law@fda.hhs.gov
Leakey, Julian	(870) 543-7916	julian.leakey@fda.hhs.gov
Lewis, Sherry	(870) 543-7627	sherrym.lewis@fda.hhs.gov
McDaniel, Lea	(870) 543-7213	lea.mcdaniel@fda.hhs.gov
Mendoza, Maria	(870) 543-7844	maria.mendoza@fda.hhs.gov
Mittelstaedt, Roberta	(870) 543-7190	roberta.mittelstaedt@fda.hhs.gov
Moon, Steven	(870) 543-7124	steven.moon@fda.hhs.gov
Nichols, Jasyl	(870) 543-7210	jasyl.nichols@fda.hhs.gov
Nysia, George	870-543-7047	nysia.george@fda.hhs.gov
Paule, Merle	(870) 543-7147	merle.paule@fda.hhs.gov
Pogribna, Marta	(870) 543-7681	marta.pogribna@fda.hhs.gov
Pogribny, Igor	(870) 543-7096	igor.pogribny@fda.hhs.gov
Siitonen, Paul	(870) 543-7656	paul.siitonen@fda.hhs.gov
Shaddock, Joseph	(870) 543-7280	joseph.shaddock@fda.hhs.gov
Stingley, Robin	(870) 543-7350	robin.stingley@fda.hhs.gov
Thorn, Brett	(870) 543-7338	brett.thorn@fda.hhs.gov
Trbojevich, Raul	(870) 543-7490	raul.trbojevich@fda.hhs.gov
Twaddle, Nathan	(870) 543-7178	nathan.twaddle@fda.hhs.gov
Vanlandingham, Michelle	(870) 543-7458	michelle.vanlandingham@fda.hhs.gov
VonTungeln, Linda	(870) 543-7620	linda.vontungeln@fda.hhs.gov
Wang, Cheng	(870) 543-7259	cheng.wang@fda.hhs.gov
Weis, Connie	(870) 543-7378	connie.weis@fda.hhs.gov
Willingham, Evelyn	(870) 543-7938	evelyn.willingham@fda.hhs.gov
Woodling, Kellie	(870) 543-7491	lkellie.woodling@fda.hhs.gov

NIEHS/NTP

Alden, Charles	(919) 541-3687	alden@niehs.nih.gov
Allen, Bonnie	(919) 541-3449	allenb@niehs.nih.gov
Alpers, Scott	(919) 541-4377	alpers@niehs.nih.gov
Andrews, Danica	(919) 541-2595	andrewsda@niehs.nih.gov
Behl, Mamta	(919) 541-2784	behlmv@niehs.nih.gov
Auerbach, Scott	(919) 541-4505	auerbachs@niehs.nih.gov
Birnbaum, Linda	(919) 541-3201	birnbaumls@niehs.nih.gov
Bishop, Jack	(919) 541-1876	bishop@niehs.nih.gov
Blystone, Chad	(919) 541-2741	blystonecr@niehs.nih.gov
Bowden, Beth	(919) 541-3355	bowden1@niehs.nih.gov
Boyd, Windy	(919) 541-9810	boydw@niehs.nih.gov
Boyle, Michael	(919) 541-1676	boylemc@niehs.nih.gov
Brown, Quashana	(919) 541-4069	brownqd@niehs.nih.gov
Bucher, John	(919) 541-4532	bucher@niehs.nih.gov
Casey, Warren	(919) 316-4729	warren.casey@nih.gov
Caspary, William	(919) 541-2150	caspary@niehs.nih.gov
Castro, Lysandra	(919) 541-3373	castro@niehs.nih.gov
Cesta, Mark	(919) 541-3229	cesta@niehs.nih.gov
Chan, Po-Chuen	(919) 541-7561	chanp@niehs.nih.gov
Chhabra, Rajendra	(919) 541-3386	chhabrar@niehs.nih.gov
Clayton, Natasha	(919) 541-7843	clayton2@niehs.nih.gov
Collins, Bradley	(919) 541-4666	collin10@niehs.nih.gov
Cora, Michelle	(1919) 316-4717	coramc@niehs.nih.gov
Corniffe, Glenda	(919) 541-4880	corniffe@niehs.nih.gov
Cunningham, Michael	(919) 541-3799	cunning1@niehs.nih.gov
Cunny, Helen	(919) 541-5717	cunnyh@niehs.nih.gov
de Serres, Frederick	(919) 541-0718	deserres@niehs.nih.gov
DeVito, Michael	(919) 541-4142	devitom@niehs.nih.gov
Di, Xudong	(919) 316-4611	dix3@niehs.nih.gov
Dixon, Darlene	(919) 541-3814	dixon@niehs.nih.gov
Dunlap, Paul	(919) 541-2679	dunlapp@niehs.nih.gov
Dunnick, June	(919) 541-4811	dunnickj@niehs.nih.gov
Elmore, Susan	(919) 541-3474	elmore@niehs.nih.gov
Fenton, Suzanne	(919) 541-4141	fentonse@niehs.nih.gov
Fields, Sally	(919) 541-3971	fields3@niehs.nih.gov
Fisher, Kristen	(919) 541-7739	fisherk2@niehs.nih.gov
Flagler, Norris	(919) 541-2397	flagler@niehs.nih.gov
Flake, Gordon	(919) 541-0037	flake@niehs.nih.gov
Foley, Julie	(919) 541-3772	foley1@niehs.nih.gov
Fostel, Jennifer	(919) 541-5055	fostel@niehs.nih.gov
Foster, Paul	(919) 541-2513	foster2@niehs.nih.gov
Frawley, Rachel	(919) 541-2151	frawleyr@niehs.nih.gov
Freedman, Jonathan	(919) 541-7899	freedma1@niehs.nih.gov
French, Jef	(919) 541-2569	french@niehs.nih.gov
Gao, Xiaohua	(919) 316-4611	gaox3@niehs.nih.gov
Germolec, Dori	(919) 541-3230	germolec@niehs.nih.gov
Guy, Robbin	(919) 541-4363	guyr2@niehs.nih.gov
Hall, Carolyn	(919) 541-4995	hall7@niehs.nih.gov
Herbert, Ronald	(919) 541-4613	herbert1@niehs.nih.gov
Hoenerhoff, Mark	(919) 541-3440	hoenerhm@niehs.nih.gov
Hong, Hue-Hua	(919) 541-2141	hong5@niehs.nih.gov
Hooth, Michelle	(919) 316-4643	hooth@niehs.nih.gov
Howdeshell, Kembra	(919) 316-4708	howdeshellkl@niehs.nih.gov
Irwin, Richard	(919) 541-3340	irwin@niehs.nih.gov
Jahnke, Gloria	(919) 541-3376	jahnke@niehs.nih.gov
Jayaram, Beby	(919) 541-1480	jayaram1@niehs.nih.gov
Jensen, Heather	(919) 541-4075	jensen1@niehs.nih.gov
Jeter, Shawn	(919) 541-3476	jeter@niehs.nih.gov
Johnson, Frank	(919) 541-3503	johnso54@niehs.nih.gov
Jones, Tina	(919) 541-2836	jones30@niehs.nih.gov
Kamel, Freya	(919) 541-1581	kamel@niehs.nih.gov
Kim, Yongbaek	(919) 316-4559	Kim16@niehs.nih.gov
Kim, Sang-Hyun	(919) 541-9468	sang-hyum.kim@nih.gov

King, Debra	(919) 541-0698	kingdh@niehs.nih.gov
King-Herbert, Angela	(919) 541-3464	kingher1@niehs.nih.gov
Kissling, Grace	(919) 541-1756	kissling@niehs.nih.gov
Koivisto, Christopher	(919) 541-3241	koivist@niehs.nih.gov
Lahousse, Stephanie	(919) 541-3069	lahousses@niehs.nih.gov
Lasko, Denise	(919) 541-0255	lasko@niehs.nih.gov
Litton, Dan	(919) 541-2100	litton@niehs.nih.gov
Lunn, Ruth	(919) 316-4637	lunn@niehs.nih.gov
Malarkey, David	(919) 541-1745	malarkey@niehs.nih.gov
Malling, Heinrich	(919) 541-3378	malling@niehs.nih.gov
Masinde, Tiwanda	(919) 541-4069	marsh2@niehs.nih.gov
Masten, Scott	(919) 541-5710	masten@niehs.nih.gov
McCarley, Deborah	(919) 541-2384	mccarley@niehs.nih.gov
McIntyre, Barry	(919) 316-4747	mcintyrebs@niehs.nih.gov
Mercado-Feliciano, Minerva	(919) 541-2756	mercadofelicim@niehs.nih.gov
Merrick, Alex	(919) 541-1531	merrick1@niehs.nih.gov
Moore, Alicia	(919) 541-7914	moore5@niehs.nih.gov
Morgan, Daniel	(919) 541-2264	morgan3@niehs.nih.gov
Ney, Elizabeth	(919) 541-5182	ney@niehs.nih.gov
Newbold, Retha	(919) 541-0738	newbold1@niehs.nih.gov
Nichols, Sharon	(919) 541-7992	nicholss2@niehs.nih.gov
Orihuela Garcia, Ruben	(919) 541-0540	ruben.orihuela@nih.gov
Ovwigho, Pamela	(919) 541-3278	ovwighope@niehs.nih.gov
Person, Rachel	919) 541-0685	rachel.person@nih.gov
Qu, Wei	919) 541-0540	qu@niehs.nih.gov
Rowley, Michael	(919) 541-3436	rowley@niehs.nih.gov
Rao, Deepa	(919) 541-0036	raod2@niehs.nih.gov
Rebolloso, Yvette	(919) 541-4209	rebollo1@niehs.nih.gov
Rice, Julie	(919) 541-2533	ricej2@niehs.nih.gov
Rider, Cynthia	(919) 541-7638	ridercv@niehs.nih.gov
Roach, Donna	(919) 541-3023	roachd@od.nih.gov
Robinson, Veronica	(919) 541-2238	godfrey@niehs.nih.gov
Rooney, Andrew	(919) 316-4704	rooneyaa@niehs.nih.gov
Roycroft, Joseph	(919) 541-3627	roycroft@niehs.nih.gov
Sanders, Michael	(919) 541-1872	sander10@niehs.nih.gov
Shelby, Michael	(919) 541-3455	shelby@niehs.nih.gov
Shockley, Keith	(919) 541-3033	shockleykr@niehs.nih.gov
Sills, Robert	(919) 541-0180	sills@niehs.nih.gov
Smith, Cynthia	(919) 541-3473	smith19@niehs.nih.gov
Soward, Sharon	(919) 541-5132	soward@niehs.nih.gov
Spencer, Diane	(919) 541-2759	spencer2@niehs.nih.gov
Stanko, Jason	(919) 541-0461	stankojp@niehs.nih.gov
Stockton, Patricia	(919) 541-4471	stockton@niehs.nih.gov
Stokes, William	(919) 541-7997	stokes@niehs.nih.gov
Stout, Matthew	(919) 541-3489	stoutm@niehs.nih.gov
Sun, Yang	(919) 541-3024	suny2@mail.nih.gov
Surh, In	(919) 541-3862	surhi@niehs.nih.gov
Sutton, Deloris	(919) 541-5112	sutton2@niehs.nih.gov
Taylor, Kyla	(919) 316-4707	taylorkw@niehs.nih.gov
Teng, Christina	(919) 541-0344	teng1@niehs.nih.gov
Thayer, Kristina	(919) 541-5021	thayer@niehs.nih.gov
Tice, Raymond	(919) 541-4482	tice@niehs.nih.gov
Tokar, Erik	(919) 541-3951	tokare@niehs.nih.gov
Ton, Thai-Vu	(919) 541-2118	ton@niehs.nih.gov
Travlos, Gregory	(919) 541-0653	travlos@niehs.nih.gov
Tubbs, Jacquelyn	(919) 541-2919	tubbsj@niehs.nih.gov
Vallant, Molly	(919) 541-5234	vallant@niehs.nih.gov
Waalkes, Michael	(919) 541-2328	waalkes@niehs.nih.gov
Waidyanatha, Suramya	(919) 541-2144	waidyanathas@niehs.nih.gov
Walker, Nigel	(919) 541-4893	walker3@niehs.nih.gov
White, Lori	(919) 541-9834	whiteld@niehs.nih.gov
Wilson, Ralph	(919) 541-4140	wilson23@niehs.nih.gov
Withers, Sheila	(919) 541-5066	withersg@niehs.nih.gov
Witt, Kristine	(919) 541-2761	witt@niehs.nih.gov
Wolfe, Mary	(919) 541-7539	wolfe@niehs.nih.gov
Wyde, Michael	(919) 316-4640	wyde@niehs.nih.gov
Yu, Xianhong	(919) 316-4599	yu1@niehs.nih.gov
Yu, Yuanyuan	(919) 541-3024	xuy5@niehs.nih.gov
Zegre-Cannon, Coralie	(919) 316-4559	cannonc@niehs.nih.gov

NIOSH/NTP

Anderson, Stacy	(304) 285-6174, X2	dbx7@cdc.gov
Beezhold, Don	(304) 285-5963	zec1@cdc.gov
Biagini, Raymond	(513) 533-8196	reb4@cdc.gov
Castranova, Vincent	(304) 285-6032	vic1@cdc.gov
Curwin, Brian	(513) 841-4432	bic4@cdc.gov
DeBord, D. Gayle	(513) 533-8212	ded4@cdc.gov
Erdely, Aaron	(304) 285-5903	efi4@cdc.gov
Estill, Cherie	(513) 841-4476	clf4@cdc.gov
Franko, Jennifer	(304) 285-6174, x8	hfy0@cdc.gov
Frasch, H. Frederick	(304) 285-5755	hbf9@cdc.gov
Geraci, Chuck	(513) 533-8339	ciu9@cdc.gov
Green, Brett	(304) 285-5884	dox6@cdc.gov
Hanley, Kevin	(513) 841-4113	kwh0@cdc.gov
Harper, Martin	(304) 285-6043	zzg7@cdc.gov
Hines, Cynthia	(513) 841-4453	cjh8@cdc.gov
Johnson, Victor	(304) 285-6249	vcj6@cdc.gov
Joseph, Pius	(304) 285-6240	pcj5@cdc.gov
Leonard, Steve	(304) 285-5831	stl0@cdc.gov
Luster, Michael	(304) 285-5940	myl6@cdc.gov
Lynch, Dennis	(513) 533-8213	dwl1@cdc.gov
Munson, Albert E.	(304) 285-6121	akm5@cdc.gov
Reynolds, Steve	(304) 285-5806	sir6@cdc.gov
Schrader, Steven	(513) 533-8210	sms4@cdc.gov
Siegel, Paul	(304) 285-5855	pds3@cdc.gov
Snawder, John	(513) 533-8496	jts5@cdc.gov
Streicher, Robert	(513) 841-4296	rps3@cdc.gov
Striley, Cynthia	(513) 533-8123	chs3@cdc.gov
Templeton, Steven	(304) 285-5721	goy6@cdc.gov
Toraason, Mark	(513) 533-8207	mht1@cdc.gov
Virji, Mohammed	(304) 285-5797	fnb8@cdc.gov
Wells, Ray	(304) 285-6341	ozw0@cdc.gov
Wurzelbacher, Steve	(513) 841-4322	srw3@cdc.gov
Yucesoy, Berran	(304) 285-5993	yab7@cdc.gov

NTP FY 2010 Publication List

Ali R, Mittelstaedt RA, Shaddock JG, Bhalli JA and Heflich RH. 2010. Micronucleus induction by Ochratoxin A in CHO and TK6 cells. *Environ Mol Mutagen* 51(7):728-728.

Ali SF, Bondy SC. 2010. Red wine but not ethanol at low doses can protect against the toxicity of methamphetamine. *Brain Res* 1346:247-250.

Anderson SE, Jackson LG, Franko J, Wells, JR. 2010. Evaluation of dicarbonyls generated in a simulated indoor air environment using an *in vitro* exposure system. *Toxicol Sci* 115(2):453-461.

Anderson SE, Munson AE, Butterworth LF, Germolec D, Morgan DL, Roycroft JA, Dill J, Meade BJ. 2010. Whole-body inhalation exposure to 1-bromopropane suppresses the IgM response to sheep red blood cells in female B6C3F1 mice and Fisher 344/N rats. *Inhal Toxicol* 22(2):125-132.

Anderson SE, Umbright C, Sellamuthu R, Fluharty K, Kashon M, Franko J, Jackson LG, Johnson VJ, Joseph, P. 2010. Irritancy and allergic responses induced by topical application of ortho-phthalaldehyde. *Toxicol Sci* 115(2):435-443.

Antonini JM, Roberts JR, Chapman RS, Soukup JM, Ghio AJ, Sriram K. 2010. Pulmonary toxicity and extrapulmonary tissue distribution of metals after repeated exposure to different welding fumes. *Inhal Toxicol* 22(10):805-816.

Antunes AMM, Godinho ALA, Martins IL, Justino GC, Beland FA, Marques, MM. 2010. Amino acid adduct formation by the nevirapine metabolite, 12-Hydroxynevirapine – a possible factor in nevirapine toxicity. *Chem Res Toxicol* 23(5):888-899.

Arias-Loza PA, Muehlfelder M, Elmore SA, Maronpot R, Hu K, Blode H, Hegele-Hartung C, Fritzemeier KH, Ertl G, Pelzer T. 2009. Differential effects of 17 beta-estradiol and of synthetic progestins on aldosterone-salt-induced kidney disease. *Toxicol Pathol* 37(7):969-982.

Auerbach SS, Bristol DW, Peckham JC, Travlos GS, Hébert CD, Chhabra RS. Toxicity and carcinogenicity studies of methylene blue trihydrate in F344N rats and B6C3F1 mice. *Food Chem Toxicol* 48(1):169-177.

Auerbach SS, Shah RR, Mav D, Smith CS, Walker NJ, Vallant MK, Boorman GA, Irwin RD. Predicting the hepatocarcinogenic potential of alkenylbenzene flavoring agents using toxicogenomics and machine learning. *Toxicol Appl Pharmacol* 243(3):300-314.

Auerbach SS, Thomas R, Shah R, Xu H, Vallant MK, Nyska A, Dunnick JK. 2010. Comparative phenotypic assessment of cardiac pathology, physiology, and gene expression in C3H/HeJ, C57BL/6J, and B6C3F1/J mice. *Toxicol Pathol* 38:923-942.

Azad N, Iyer A, Vallyathan V, Wang L, Castranova V, Stehlik C, Rojanasakul Y. 2010. Role of oxidative/nitrosative stress-mediated Bcl-2 regulation in apoptosis and malignant transformation. *Ann N Y Acad Sci* 1203:(1-6).

Azad N, Iyer AKV, Wang LY, Lu YJ, Medan D, Castranova V, Rojanasakul Y. 2010. Nitric oxide-mediated Bcl-2 stabilization potentiates malignant transformation of human lung epithelial cells. *Am J Respir Cell Mol Biol* 42(5):578-585.

Bach U, Hailey JR, Hill GD, Kaufmann W, Latimer KS, Malarkey DE, Maronpot RM, Miller RA, Moore RR, Morrison JP, Nolte T, Rinke M, Rittinghausen S, Suttie RW, Travlos GS, Vahle JL, Willson GA and Elmore SA. 2010. Proceedings of the 2009 National Toxicology Program satellite symposium. *Toxicol Pathol* 38(1):9-36.

Barnard DE, Lewis SM, Teter BB, Thigpen JE. 2009. Open- and closed-formula laboratory animal diets and their importance to research. *J Am Assoc Lab Anim Sci* 48(6):709-713.

Bauer AK, Fostel J, Degraff LM, Rondini EA, Walker C, Grissom SF, Foley J, Kleeberger SR. 2009. Transcriptomic analysis of pathways regulated by toll-like receptor 4 in a murine model of chronic pulmonary inflammation and carcinogenesis. *Mol Cancer* 8:107.

Beezhold KJ, Castranova V, Chen F. 2010. Microprocessor of microRNAs: regulation and potential for therapeutic intervention. *Mol Cancer* 9:134.

Beland FA. 2009. Abstracts of the 32nd Annual Meeting of the United Kingdom Environmental Mutagen Society, 12-15 July 2009 at the University of Leeds, UK. *Mutagenesis* 24(6):523-523.

Bell DR, Clode S, Fan MQ, Fernandes A, Foster PMD, Jiang T, Loizou G, MacNicoll A, Miller BG, Rose M, Tran L and White S. 2010. Interpretation of studies on the developmental reproductive toxicology of 2,3,7,8-tetrachlorodibenzo-p-dioxin in male offspring. *Food Chem Toxicol* 48(6):1439-1447.

Benbrahim-Tallaa L, Tokar EJ, Diwan BA, Coppin JF, Waalkes MP. 2009. Cadmium malignantly transforms normal human breast epithelial cells into a basal-like phenotype. *Environ Health Perspect* 117(12):1847-1852.

Bhalli JA, Dobrovolsky VN, Heflich RH. 2010. Pig-a mutation manifestation in mice following single and split doses of N-ethyl-N-nitrosourea. *Environ Mol Mutagen* 51(7):722-722.

B'Hymer C, Cheever KL. 2010. Evaluation of a procedure for the simultaneous quantification of 4-ketocyclophosphamide, cyclophosphamide, and Ifosfamide in human urine. *J Chromatogr Sci* 48(5):328-333.

Binienda ZK, Ross IA, Gough B, Riccio T, Kim CS, Ali SF. Striatal dopamine in the response of brain and liver unsaturated and saturated free fatty acids following administration of C75 in CD-1 mice. *Neurosci Lett* 469(3):324-327.

Binienda ZK, Beaudoin MA, Gough B, Ali SF, Virmani A. 2010. Assessment of 3-nitropropionic acid-evoked peripheral neuropathy in rats: neuroprotective effects of acetyl-l-carnitine and resveratrol. *Neurosci Lett* 480(2):117-121.

Birnbaum LS, Zenick H, Branche CM. 2009. Environmental justice: a continuing commitment to an evolving concept. Am J Public Health Suppl 3:S487-9. Erratum in: *Am J Public Health*. 2010 Feb;100(2):199.

Birnbaum LS. 2009. Applying research to public health questions: timing and the environmentally relevant dose. *Environ Health Perspect* 117(11):A478.

Birnbaum LS. 2009. NIEHS supports partnerships in environmental public health. *Prog Community Health Partnersh* 3(3):195-196.

Blanco I, Janciauskiene S, Nita I, Fernandez-Bustillo E, Carcaba V, Gallo C, Alvarez-Rico M, de Serres F, Beridze N. 2010. Low plasma levels of monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-alpha (TNF), and vascular endothelial growth factor (VEGF) in patients with alpha1-antitrypsin deficiency-related fibromyalgia. *Clin Rheumatol* 29(2):189-197.

Blanco IB, Astudillo A, Iglesias FD, Janciauskiene S, Fernandez VC, Alvaro CG, Argiz HC, de Serres FJ, Bustillo, EF. 2010. Intravenous infusions of purified alpha-1 antitripsyn effectively controls symptoms and reverts muscle biopsy changes in an MZ alpha-1 antitripsyn deficiency and fibromyalgia syndrome Patient. *J Musculoskelet Pain* 18(2):167-172.

Blystone CR, Kissling GE, Bishop JB, Chapin RE, Wolfe GW, Foster PM. 2010. Determination of the di-(2-ethylhexyl) phthalate NOAEL for reproductive development in the rat: importance of the retention of extra animals to adulthood. *Toxicol Sci* 116(2):640-646.

Borm P, Castranova V. 2009. Toxicology of nanomaterials: permanent interactive learning. *Part Fibre Toxicol* 6:28.

Bowman JD, Miller CK, Krieg EF, Song RG. 2010. Analyzing digital vector waveforms of 0-3000 Hz magnetic fields for health studies. *Bioelectromagnetics* 31(5):391-405.

Boyd WA, Crocker TL, Rodriguez AM, Leung MCK, Wade Lehmann D, Freedman JH, Van Houten B, Meyer JN. 2010. Nucleotide excision repair genes are expressed at low levels and are not detectably inducible in Caenorhabditis elegans somatic tissues, but their function is required for normal adult life after UVC exposure. *Mutat Res* 683 (1-2):57-67.

Boyd WA, McBride SJ, Rice JR, Snyder DW, Freedman JH. 2010. A high-throughput method for assessing chemical toxicity using a Caenorhabditis elegans reproduction assay. *Toxicol Appl Pharmacol* 245(2):153-159.

Burch JB, Svendsen E, Siegel PD, Wagner SE, Von Essen S, Keefe T, Mehaffy J, Martinez AS, Bradford M, Baker L, Cranmer B, Saito R, Tessari J, Linda P, Andersen C, Christensen O, Koehncke N, Reynolds SJ. 2010. Endotoxin exposure and inflammation markers among agricultural workers in Colorado and Nebraska. *J Toxicol Environ Health A* 73(1):5-22.

Caldwell J, Lunn R, Ruder A. 2010. Trichloroethylene. In identification of research needs to resolve the carcinogenicity of high-priority IARC carcinogens. Views and expert opinions of an IARC/NORA expert group meeting, Lyon, France, 30 June – 2 July 2009. *IARC Technical Publication* No. 42.

Caldwell J, Lunn R. 2010. Dichloromethane, methylene chloride (DCM). In identification of research needs to resolve the carcinogenicity of high-priority IARC carcinogens. Views and expert opinions of an IARC/NORA expert group meeting, Lyon, France, 30 June – 2 July 2009. *IARC Technical Publication* No. 42

Cannon CZ, Godfrey VL, King-Herbert A, Nielsen JN. 2009. Metastatic uterine adenocarcinoma in an 8-year-old gilt. *J Am Assoc Lab Anim Sci* 48(6):795-800.

Cao LY, Taylor JS, Sood A, Murray D, Siegel PD. 2010. Allergic contact dermatitis to synthetic rubber gloves: Changing trends in patch test reactions to accelerators. *Arch Dermatol* 146(9):1001-1007.

Card JW, Carey MA, Voltz JW, Bradbury JA, Ferguson CD, Cohen EA, Schwartz S, Flake GP, Morgan DL, Arbes Jr SJ, Barrow DA, Barros SP, Offenbacher S, Zeldin, DC. 2010. Modulation of allergic airway inflammation by the oral pathogen Porphyromonas gingivalis. *Infect Immun* 78(6):2488-2496.

Carey MA, Bradbury JA, Rebolloso YD, Graves JP, Zeldin DC, Germolec DR. 2010. Pharmacologic inhibition of COX-1 and COX-2 in influenza A viral infection in mice. *PLoS One* 5(7):e11610.

Carreon T, Hein MJ, Viet S, Hanley KW, Ruder AM, Ward EM. 2009. Increased bladder cancer risk among workers exposed to o-toluidine and aniline: a reanalysis. *Occup Environ Med* 67:348-350.

Castranova V, Fedan J. 2010. Dr. Val Vallyathan: In memoriam. *Part Fibre Toxicol* 7:24

Cederroth CR, Zimmermann C, Beny JL, Schaad O, Combepine C, Descombes P, Doerge DR, Pralong FP, Vassalli JD, Nef S. 2010. Potential detrimental effects of a phytoestrogen-rich diet on male fertility in mice. *Mol Cell Endocrinol* 321(2):152-160.

Cesta MF, Ryman-Rasmussen JP, Wallace DG, Masinde T, Hurlburt G, Taylor AJ, Bonner JC. 2010. Bacterial lipopolysaccharide enhances PDGF signaling and pulmonary fibrosis in rats exposed to carbon nanotubes. *Am J Respir Cell Mol Biol* 43(2):142-151.

Chambliss KL, Wu QA, Oltmann S, Konaniah ES, Umetani M, Korach KS, Thomas GD, Mineo C, Yuhanna IS, Kim SH, Madak-Erdogan Z, Maggi A, Dineen SP, Roland CL, Hui DY, Brekken RA, Katzenellenbogen JA, Katzenellenbogen BS, Shaul, PW. 2010. Non-nuclear estrogen receptor alpha signaling promotes cardiovascular protection but not uterine or breast cancer growth in mice. *J Clin Invest* 120(7):2319-2330.

Chan PC, IARC Working Group. 2010. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Ingested nitrates and nitrites, and cyanobacterial peptide toxins. *Lyon, France*. Vol 4 *http://monographs.iarc.fr/ENG/Monographs/vol94/index.php*

Chan PC, Ramot Y, Malarkey DE, Blackshear P, Kissling G, Travlos G, Nyska A. 2010. 14-Weeks toxicity study of green tea extract in rats and mice. *Toxicol Pathol* 38:1070-1084.

Chandra SA, Nolan MW, Malarkey DE. 2010. Chemical carcinogenesis of the gastrointestinal tract in rodents: An overview with emphasis on NTP carcinogenesis bioassays. *Toxicol Pathol* 38(1):188-197.

Chang Q, Pan J, Wang X, Zhang Z, Chen F, Shi X. 2010. Reduced reactive oxygen species-generating capacity contributes to the enhanced cell growth of arsenic-transformed epithelial cells. *Cancer Res* 70(12):5127-5135.

Chelonis J, Johnson T, Ferguson S, Kubacak B, Edwards M, Paule M. 2010. Effects of methylphenidate on motivation in children with attention-deficit/hyperactivity disorder. *Neurotoxicol Teratol* 32(4):504.

Chen F, Li S, Castanova V. 2009. Signature genes for both hepatoblastoma and hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 21(10):1220-1221.

Chen F, Li S, Castranova V. 2009. Overlapping signature genes between hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Eur J Gastroenterol Hepatol* 21(11):1320-1321.

Chen T, Mei N, Fu PP. 2010. Genotoxicity of pyrrolizidine alkaloids. *J Appl Toxicol* 30(3):183-96.

Chiang HM, Yin JJ, Xia Q, Zhao Y, Fu PP, Wen KC, Yu H. 2010. Photoirradiation of azulene and guaiazulene-Formation of reactive oxygen species and induction of lipid peroxidation. *J Photochem Photobiol A Chem* 211(2-3):123-128.

Chipinda I, Ajibola RO, Morakinyo MK, Ruwona TB, Simoyi RH, Siegel PD. 2010. Rapid and simple kinetics screening assay for electrophilic dermal sensitizers using nitrobenzenethiol. *Chem Res Toxicol* 23(5):918-25.

Cimafranca MA, Davila J, Ekman GC, Andrews RN, Neese SL, Peretz J, Woodling KA, Helferich WG, Sarkar J, Flaws JA, Schantz SL, Doerge DR, Cooke PS. 2010. Acute and chronic effects of oral genistein administration in neonatal mice. *Biol Reprod* 83(1):14-121.

Collins BJ, Stout MD, Levine KE, Kissling GE, Melnick RL, Fennell TR, Walden R, Pritchard JB, Fernando RA, Burka LT, and Hooth MJ. 2010. Exposure to hexavalent chromium resulted in significantly higher tissue chromium burden compared with trivalent chromium following similar oral doses to male F344/N rats and female B6C3F1 mice. *Tox Sci* 118(2):368-379.

Cowin PA, Gold E, Aleksova J, O'Bryan MK, Foster PM, Scott HS, Risbridger GP. 2010. Vinclozolin exposure *in utero* induces postpubertal prostatitis and reduces sperm production via a reversible hormone-regulated mechanism. *Endocrinology* 151:783-792.

Crawford LW, Foley JF, Elmore SA. 2010. Histology atlas of the developing mouse hepatobiliary system with emphasis on E9.5 to E18.5. *Toxicol Pathol* 38:872-906.

Cruz VPDL, Elinos-Calderón D, Carrillo-Mora P, Silva-Adaya D, Konigsberg M, Morán J, Ali SF, Chánez-Cárdenas ME, Pérez-De La Cruz G, Santamaría A. 2010. Time-course correlation of early toxic events in three models of striatal damage: modulation by proteases inhibition. *Neurochem Int* 56(6-7):834-842.

Cuevas E, Lantz S, Newport G, Divine B, Wu Q, Paule MG, Tobón-Velasco JC, Ali SF, Santamaría A. 2010. On the early toxic effect of quinolinic acid: involvement of RAGE. *Neurosci Lett* 474(2):74-78.

Cummings KJ, Gaughan DM, Kullman GJ, Beezhold DH, Green BJ, Blachere FM, Bledsoe T, Kreiss K, Cox-Ganser J. 2010. Adverse respiratory outcomes associated with occupational exposures at a soy processing plant. *Eur Respir J* 36(5)1007-1015.

Cunningham ML, Collins BJ, Hejtmancik MR, Herbert RA, Travlos GS, Vallant MK, Stout MD. 2010. Effects of the PPAR alpha agonist and widely used antihyperlipidemic drug gemfibrozil on hepatic toxicity and lipid metabolism. *PPAR Res* 2010:681963.

Curwin BD, Hein MJ, Barr DB, Striley C. 2010. Comparison of immunoassay and HPLC-MS/MS used to measure urinary metabolites of atrazine, metolachlor, and chlorpyrifos from farmers and non-farmers in Iowa. *J Expo Sci Environ Epidemiol* 20(2):205-212.

Davis RR, Custer DA, Krieg E, Alagramam K. 2010. N-Acetyl L-cysteine does not protect mouse ears from the effects of noise. *J Occup Med Toxicol* 5:11.

DeBord DG, Schulte P, Butler MA, McCanlies E, Reutman S, Ruder A, Schill A, Schubauer-Berigan M, Schuler C, Weston A. 2009. Genetics in the Workplace: Implications for Occupational Safety and Health. Washington, DC: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2010-101.

De Serres FJ, Blanco I, Fernández-Bustillo E. 2010. Ethnic differences in alpha-1 antitrypsin deficiency in the United States of America. *Ther Adv Respir Dis* 4(2):63-70.

Dertinger SD, Phonethepswath S, Weller P, Stankowski LF, Roberts DJ, Shi J, Krsmanovic L, Vohr HW, Custer L, Gleason C, Henwood A, Sweder K, Giddings A, Lynch AM, Gunther WC, Thiffeault CJ, Shutsky TJ, Fiedler RD, Bhalli JA, Heflich RH. 2010. Pig-a Mutation assay: Evaluation of inter-laboratory transferability and reproducibility. *Environ Mol Mutagen* 51(7):P86.

Dietert RR, DeWitt JC, Germolec DR, Zelikoff JT. 2010. Breaking patterns of environmentally influenced disease for health risk reduction: immune perspectives. *Environ Health Perspect* 118(8):1091-1099.

Ding M, Zhao J, Bowman L, Lu Y, Shi X. 2010. Inhibition of AP-1 and MAPK signaling and activation of Nrf2/ARE pathway by quercitrin. *Int J Oncol* 36(1):59-67.

Dinse GE, Peddada SD, Harris SF, Elmore SA. 2010. Comparison of NTP historical control tumor incidence rates in female Harlan Sprague Dawley and Fischer 344/N rats. *Toxicol Pathol* 38(5):765-775.

Dobrovolsky VN, Shaddock JG, Pearce MG, Heflich RH. 2010. Differential Induction of Pig-a and Hprt mutation following exposure of rats to ionizing radiation. *Environ Mol Mutagen* 51(7): 724-724.

Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW. 2010. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. *Toxicol Appl Pharmacol* 247(2):158-65.

Draper DW, Madenspacher JH, Dixon D, King DH, Remaley AT, Fessler MB. 2010. ATP-binding cassette transporter G1 deficiency dysregulates host defense in the lung. *Am J Respir Crit Care Med* 182(3):404-12.

Elmore S A. 2010. Enhanced histopathology evaluation of lymphoid organs. In: Methods in Molecular Biology; Immunotoxicity Testing (Humana Press). Ed. Dietert R. Chapter 22:323-339.

Fan X, Lobenhofer EK, Chen M, Shi W, Huang J, Luo J, Zhang J, Walker SJ, Chu TM, Li L, Wolfinger R, Bao W, Paules RS, Bushel PR, Li J, Shi T, Nikolskaya T, Nikolsky Y, Hong H, Deng Y, Cheng Y, Fang H, Shi L. Tong W. 2010. Consistency of predictive signature genes and classifiers generated using different microarray platforms. *Pharmacogenomics J* 10(4):247-257.

Fang F, Xu Q, Park Y, Huang XM, Hollenbeck A, Blair A, Schatzkin A, Kamel F, Chen HL. 2010. Depression and the subsequent risk of Parkinson's disease in the NIH-AARP Diet and Health Study. *Mov Disord* 25(9):1157-1162.

Fang JL, Stingley RL, Beland FA, Harrouk W, Lumpkins DL, Howard P. 2010. Occurrence, efficacy, metabolism, and toxicity of triclosan. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 28(3):147-171.

Fedan JS, Piedimonte G. 2010. Dr. R Shiffmann's Asthmador: relevant to our times, or a snake oil remedy? *Curr Opin Pharmacol* 10(3):213-217.

Fenton SC, Rudel RA, Euling SY, Makris SL. 2010. Mammary gland development as a sensitive indicator of early life exposures: recommendations from an interdisciplinary workshop. Birth Defects Res *A Clin Mol Teratol* 88(5):359-359.

Ferguson SA, Berry KJ. 2010. Chronic oral treatment with isotretinoin alters measures of activity but not anxiety in male and female rats. *Neurotoxicol Teratol* 32(5):573-578.

Ferguson SA, Boctor SY. 2010. Cocaine responsiveness or anhedonia in rats treated with methylphenidate during adolescence. *Neurotoxicol Teratol* 32(4):432-442.

Ferguson SA, Garey J, Smith ME, Twaddle NC, Doerge DR, Paule MG. 2010. Preweaning behaviors, developmental landmarks, and acrylamide and glycidamide levels after pre- and postnatal acrylamide treatment in rats. *Neurotoxicol Teratol* 32(3):373-382.

Foster PMD. 2010. The cons of the extended one-generation study protocol. *Birth Defects Res A Clin Mol Teratol* 88(5):325.

Fowler BA, Schubauer-Berigan M, Hines CJ. 2010. Indium phosphide and other indium compounds: includes indium phosphide, indium arsenide, indium tin oxide, CIS, CIGS. In Identification of Research Needs to Resolve the Carcinogenicity of High-priority IARC Carcinogens. Views and Expert Opinions of an IARC/NORA Expert Group Meeting, Lyon, France, 30 June – 2 July 2009. IARC Technical Publication No. 42. *Lyon, France: International Agency for Research on Cancer* 42:16-24.

French J E, Leblanc B, Long GG, Morton D, Storer R, Leighton J, Swenburg J, Tsuda H. Panel discussion: alternative mouse models for carcinogenicity assessment. *Toxicol Pathol* 38(1):72-5.

Gamboa da Costa G, Singh R, Arit VM, Mirza A, Richards M, Takamura-Enya T, Schmeiser HH, Farmer PB, Phillips DH. 2009. Quantification of 3-nitrobenzanthrone-DNA adducts using online column-switching HPLC-electrospray tandem mass spectrometry. *Chem Res Toxicol* 22(11):1860-1868.

Gao X, Yu L, Castro L, Moore AB, Hermon T, Bortner C, Sifre M, Dixon D. 2010. An endocrine-disrupting chemical, fenvalerate, induces cell cycle progression and collagen type I expression in human uterine leiomyoma and myometrial cells. *Toxicol Lett* 196(3):133-141.

Garey J, Binienda Z, Paule M. 2010. Effect of lifetime exposure to acrylamide on motor nerve conduction velocity in rats at one year of age. *Neurotoxicol Teratol* 32(4):504-505.

Germolec DR, Frawley RP, Evans E. 2010. Markers of inflammation. *Methods Mol Biol* 598:53-73.

Ghosh S, Hoenerhoff MJ, Clayton N, Myers P, Stumpo DJ, Maronpot RR, Blackshear PJ. 2010. Left-sided cardiac valvulitis in tristetraprolin-deficient mice: the role of tumor necrosis factor alpha. *Am J Pathol* 176(3):1484-1493.

Glass R, Rosenthal J, Jessup CM, Birnbaum L, Portier C. 2009 Tackling the research challenges of health and climate change. *Environ Health Perspect* 117(12):A534.

Godin SJ, DeVito MJ, Hughes MF, Ross DG, Scollon EJ, Starr JM, Setzer RW, Conolly RB, Tornero-Velez R. 2010. Physiologically based pharmacokinetic modeling of deltamethrin: development of a rat and human diffusion-limited model. *Toxicol Sci* 115(2):330-343.

Gohlke JM, Stockton PS, Sieber S, Foley J, Portier CJ. 2009. AhR-mediated gene expression in the developing mouse telencephalon. *Reprod Toxicol* 28(3):321-328.

Goodman JI, Augustine KA, Cunnningham ML, Dixon D, Dragan YP, Falls JG, Rasoulpour RJ, Sills RC, Storer RD, Wolf DC, Pettit SD. 2010. What do we need to know prior to thinking about incorporating an epigenetic evaluation into safety assessments? *Toxicol Sci* 116(2):375-381.

Grajewski B, Waters MA, Yong LC, Tseng CY, Zivkovich Z, Cassinelli RT. 2010. Airline pilot cosmic radiation and circadian disruption exposure assessment from logbooks and company records. *Am J Epidemiol* 171(S86-S86)

Green BJ, Tovey ER, Beezhold DH, Perzanowski MS, Acosta LM, Divjan AI, Chew GL. 2009. Surveillance of fungal allergic sensitization using the fluorescent halogen immunoassay. *J Mycol Med* 19(4):253-261.

Guo L, Dial S, Shi Q, Xia Q, Mei N, Li Q, Chan PC, Fu P. 2010. Gene expression profiling in male B6C3F1 mouse livers exposed to kava identifies - changes in drug metabolizing genes and potential mechanisms linked to kava toxicity. *Food Chem Toxicol* 48, 686-696.

Guo L, Mei N, Liao W, Chan PC, Fu P. 2010. Ginkgo biloba extract induces gene expression changes in xenobiotics metabolism and the Myc-centered network. *OMICS J Int Biol* 14:75-90.

Guo L, Mei N, Xia QS, Chen T, Chan PC, Fu PP. 2010. Gene expression profiling as an initial approach for mechanistic studies of toxicity and tumorigenicity of herbal plants and herbal dietary supplements. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 28(1):60-87.

Guo, L, Shi Q, Dial S, Xia Q, Mei N, Li QZ, Chan PC, Fu P. Gene expression profiling in male B6C3F1 mouse livers exposed to kava identifies changes in drug metabolizing genes and potential mechanisms linked to kava toxicity. *Food Chem Toxicol* 48(2):686-696.

Hakk H, Diliberto JJ, Birnbaum LS. 2009. The effect of dose on 2,3,7,8-TCDD tissue distribution, metabolism and elimination in CYP1A2 (-/-) knockout and C57BL/6N parental strains of mice. *Toxicol Appl Pharmacol* 241(1):119-126.

Hamilton RF, Wu N, Porter D, Buford M, Wolfarth M, Holian A. 2009. Particle length-dependent titanium dioxide nanomaterials toxicity and bioactivity. *Part Fibre Toxicol* 6:35.

Hanley KW, Petersen MR, Cheever KL, Luo L. 2010. Bromide and N-acetyl-S-(n-propyl)-L-cysteine in urine from workers exposed to 1-bromopropane solvents from vapor degreasing or adhesive manufacturing. *Int Arch Occup Environ Health* 83(5):571-84.

Hard, GC, Flake GP, Sills RC. 2009. Re-evaluation of kidney histopathology from 13-week toxicity and two-year carcinogenicity studies of melamine in the F344 rat: Morphologic evidence of retrograde nephropathy. *Vet Pathol* 46(6):1248-1257.

Harrison JC, Ham JE. 2009. βIonone reactions with the nitrate radical: Rate constant and gas-phase products. *Int J Chem Kinetics* 41(10):629-641.

Hein MJ, Waters MA, Ruder AM, Stenzel MR, Blair A, Stewart PA. 2010. Statistical modeling of occupational chlorinated solvent exposures for case-control studies using a literature-based database. *Ann Occup Hyg* 54(4):459-472.

Hines CJ, Yau AY, Zuniga MM, Wells JR, Nilsen Hopf NB, Camann DE. Development of a personal dual-phase air sampling method for phthalate diesters. *J Environ Monit* 12(2):491-499.

Hines, CJ, Hopf NB, Deddens JA, Silva MJ, Calafat AM. 2009. Estimated daily intake of phthalates in occupationally exposed groups. *J Expo Sci Environ Epidemiol* 21(2):133-141.

Hladik WJ, Stover J, Esiru G, Harper M, Tappero J. 2009. The contribution of family planning towards the prevention of vertical HIV transmission in Uganda. *PLoS One* 4(11):e7691.

Hobbs CA, Recio L, Shepard K, Green A, Winters J, Baldetti C, Streicker M, Witt KL. 2010. Genotoxicity of hydroxyurea in mice measured at doses relevant to pediatric sickle cell anemia patients. *Environ Mol Mutagen* 51(7):727.

Hoenerhoff MJ, Hong HH, Ton T, Lahousse SA, Sills RC. 2009. A review of the molecular mechanisms of chemically induced neoplasia in rat and mouse models in national toxicology program bioassays and their relevance to human cancer. *Toxicol Pathol* 37(7):835-848.

Hoffler U, Hobbie K, Wilson R, Bai R, Rahman A, Malarkey D, Travlos G, Ghanayem BI. 2009. Diet-induced obesity is associated with hyperleptinemia, hyperinsulinemia, hepatic steatosis, and glomerulopathy in C57Bl/6J mice. *Endocrine* 36(2):311-325.

Hopf NB, Ruder AM, Succop P. 2009. Background levels of polychlorinated biphenyls in the U.S. population. *Sci Total Environ* 407(24):6109-6119.

Hopf NB, Waters MA, Ruder AM, Prince MM. 2010. Development of a retrospective job exposure matrix for PCB-exposed workers in capacitor manufacturing. *J Occup Health* 52(4):199-208.

Hotchkiss AK, Rider CV, Furr J, Howdeshell KL, Blystone CR, Wilson VS, Gray Jr LE. 2010. *In utero* exposure to an AR antagonist plus an inhibitor of fetal testosterone synthesis induces cumulative effects on F1 male rats. *Reprod Toxicol* 30(2):261-270.

Huff J, Chan P, Melnick R. 2010. Clarifying carcinogenicity of ethylbenzene. *Reg Toxicol Pharmacol* 58, 167-169.

Jefferson WN, Doerge D, Padilla-Banks E, Woodling KA, Kissling GE, Newbold R. 2009. Oral exposure to genistin, the glycosylated form of genistein, during neonatal life adversely affects the female reproductive system. *Environ Health Perspec* 117(12):1883-1889.

John K, Churchwell MI, Beland FA, Pratt MM, McMullen G, Poiner MC. 2010. Chlorophyllin (CHL) differentially modulates benzo(a)pyrene-DNA (BP-DNA) adduct formation in C57BL16 mice chronically fed BP and CHL in the diet. *Environ Mol Mutagen* 51(7):720.

Kagan VE, Wipf P, Stoyanovsky D, Greenberger JS, Borisenko G, Belikova NA, Yanamala N, Samhan Arias AK, Tungekar MA, Jiang J, Tyurina YY, Ji J, Klein-Seetharaman J, Pitt BR, Shvedova AA, Bayir H. 2009. Mitochondrial targeting of electron scavenging antioxidants: Regulation of selective oxidation vs random chain reactions. *Adv Drug Deliv Rev* 61(14):1375-1385.

Kagan VE, Konduru NV, Feng W, Allen BL, Conroy J, Volkov Y, Vlasova II, Belikova NA, Yanamala N, Kapralov A, Tyurina YY, Shi J, Kisin ER, Murray AR, Franks J, Stolz D, Gou P, Klein-Seetharaman J, Fadeel B, Star A, Shvedova AA. 2010. Carbon nanotubes degraded by neutrophil myeloperoxidase induce less pulmonary inflammation. *Nat Nanotechnol* 5(5):354-359.

Kagan VE, Shi J, Feng W, Shvedova AA ,Fadeel B. 2010. Fantastic voyage and opportunities of engineered nanomaterials: what are the potential risks of occupational exposures? *J Occup Environ Med* 52(9):943-946.

Kamel F, Bhudhikanok G, Blair A, Goldman S, Hoppin J, Korell M, Langston JW, Richards M, Ross GW, Webster G, Sandler D, Umbach D, Tanner C. 2009. Pesticide exposure and Parkinson's disease (PD) in the Agricultural Health Study (AHS). *Epidemiol* 20(6):S244-S244.

Kang HS, Kim YS, ZeRuth G, Beak JY, Gerrish K, Kilic G, Sosa-Pineda B, Jensen J, Pierreux CE, Lemaigre FP, Foley J, Jetten AM. 2009. Transcription factor Glis3, a novel critical player in the regulation of pancreatic beta-cell development and insulin gene expression. *Mol Cell Biol* 29(24):6366-6379.

Kang-Sickel JC, Stober VP, French JE, Nylander-French LA. 2010. Exposure to naphthalene induces naphthyl-keratin adducts in human epidermis *in vitro* and *in vivo*. *Biomarkers* 15(6):488-497.

Ke H, Parron VI, Reece J, Zhang JY, Akiyama SK, French JE. 2010. BCL2 inhibits cell adhesion, spreading, and motility by enhancing actin polymerization. *Cell Res* 20(4):458-469.

Keane M, Stone S, Chen B. 2010. Welding fumes from stainless steel gas metal arc processes contain multiple manganese chemical species. *J Environ Monit* 12(5):1133-1140.

Kim YS, Harry GJ, Kang HS, Goulding D, Wine RN, Kissling GE, Liao G, Jetten AM. 2010. Altered cerebellar development in nuclear receptor TAK1/TR4 null mice is associated with deficits in GLAST(+) glia, alterations in social behavior, motor learning, startle reactivity, and microglia. *Cerebellum* 9(3):310-323.

King-Herbert A, Sills R, Bucher J. 2010. Commentary: update on animal models for NTP studies. *Toxicol Pathol* 38(1):180-181.

Kirby A, Kang HM, Wade CM, Cotsapas C, Kostem E, Han B, Furlotte N, Kang EY, Rivas M, Bogue MA, Frazer KA, Johnson FM, Beilharz EJ, Cox DR, Eskin E, Daly MJ. 2010. Fine mapping in 94 inbred mouse strains using a high-density haplotype resource. *Genetics* 185(3):1081-1095.

Kodavanti PRS, Coburn CG, Moser VC, MacPhail RC, Fenton SE, Stoker TE, Rayner JL, Kannan K, Birnbaum LS. 2010. Developmental exposure to a commercial PBDE mixture, DE-71: neurobehavioral, hormonal, and reproductive effects. *Toxicol Sci* 116(1):297-312.

Kojima C, Ramirez DC, Tokar EJ, Himeno S, Drobná Z, Stýblo M, Mason RP, Waalkes MP. 2009. Requirement of arsenic biomethylation for oxidative DNA damage. *J Natl Cancer Inst* 101(24):1670-1681.

Kostyal D, Horton K, Beezhold D, Lockwood S, Hamilton RG. 2009. Latex as a significant source of Hevea brasiliensis allergen exposure. *Ann Allergy Asthma Immunol* 103(4):354-355.

Krieg EF, Butler MA, Chang MH, Liu TB, Yesupriya A, Dowling N, Lindegren ML and for the CDC/NCI NHANES III Genomics Working Group. 2010. Lead and cognitive function in VDR genotypes in the third National Health and Nutrition Examination Survey. *Neurotoxicol Teratol* 32(2):262-272.

Law BF, Hettick JM, Hornsby-Myers J, Siegel PD. 2010. Analytical methodology and assessment of potential second-hand exposure to fentanyl in the hospital surgical setting. *J Addict Dis* 29(1):51-58.

Law BF, Hettick JM, Hornsby-Myers J, Siegel PD. (2010). Reservations concerning second-hand fentanyl exposure in the operating room. *J Addict Dis* 29(3):282-283.

Lea IA, Jackson MA, Dunnick JK. 2009. Genetic pathways to colorectal cancer. *Mutat Res/Fundamental Mol Mech Mut* 670(1-2):96-98.

Leblanc AJ, Moseley AM, Chen BT, Frazer D, Castranova V, Nurkiewicz TR. 2010. Nanoparticle inhalation impairs coronary microvascular reactivity via a local reactive oxygen species-dependent mechanism. *Cardiovasc Toxicol* 10(1):27-36.

Lee CR, Imig JD, Edin ML, Foley J, Degraff LM, Bradbury JA, Graves JP, Lih FB, Clark J, Myers P, Perrow AL, Lepp AN, Kannon MA, Ronnekleiv OK, Alkayed NJ, Falck JR, Tomer KB, Zeldin DC. 2010. Endothelial expression of human cytochrome P450 epoxygenases lowers blood pressure and attenuates hypertension-induced renal injury in mice. *FASEB J* 24(10)3770-3781.

Lee EG, Nelson J, Hintz PJ, Joy G, Andrew ME, Harper M. (2010). Field performance of the CATHIA-T sampler and two cyclones against the standard Cowled sampler for thoracic fiber concentrations. *Ann Occup Hyg* 54(5):545-556.

Lee T, Kim SW, Chisholm WP, Slaven J, Harper M. 2010. Performance of high flow rate samplers for respirable particle collection. *Ann Occup Hyg* 54(6):697-709.

Levine KE, Stout MD, Ross GT, Essader AS, Weber FX, Grohse PM, Fernando RA, Milstein LS, Hooth MJ, Collins BJ. 2010. Validation and application of a method for the determination of total chromium in rat tissues by inductively coupled plasma mass spectrometry. *Arch Environ Contam Toxicol* 58(3):883-891.

Levis S, Strickman-Stein N, Doerge DR, Krischer J. 2010. Design and baseline characteristics of the Soy Phytoestrogens As Replacement Estrogen (SPARE) study - A clinical trial of the effects of soy isoflavones in menopausal women. *Contemp Clin Trials* 31(4):293-302.

Levy DD, McDaniel LP, Witt KL. 2010. Sensitivity and specificity of the *in vivo* rodent micronucleus assay towards the detection of rodent carcinogens. An updated analysis of National Toxicology Program data. *Environ Mol Mutagen* 51(7):731.

Lewis SM, Lee FW, Ali AA, Allaben WT, Weis CC, Leakey JEA. 2010. Modifying a displacement pump for oral gavage dosing of solution and suspension preparations to adult and neonatal mice. *Lab Animal* 39(5):149-154.

Li Y, Birnbaumer L, Teng CT. 2010. Regulation of ERRβgene expression by estrogen receptor agonists and antagonists in SKBR3 breast cancer cells: differential molecular mechanisms mediated by G protein-coupled receptor GPR30/GPER-1. *Mol Endocrinol* 24(5):969-980.

Lin G, Li N, Li M, Chan WY, Fu PP, Xu HX. 2010. Potential biomarker for the assessment of hepatotoxicity induced by metabolic activation of pyrrolizidine alkaloids. *Drug Metab Rev* 42(207-207) Abstract P314.

Lin MI, Groves WA, Freivalds A, Lee L, Lee EG, Slaven JE, Harper M. 2010. Laboratory evaluation of a physiologic sampling pump (PSP). *J Environ Monit* 12(7):1415-1421.

Liu F, Zou X, Sadovova N, Zhang X, Shi L, Guo L, Qian F, Wen Z, Patterson TA, Hanig JP, Paule MG, Slikker W Jr, Wang C. 2010. Changes in gene expression after phencyclidine administration in developing rats: a potential animal model for schizophrenia. *Int J Dev Neurosci* 2010 Aug5 Epub ahead of print.

Liu JL, Yu L, Coppin JF, Tokar EJ, Diwan BA, Waalkes MP. 2009. Fetal arsenic exposure appears to facilitate endocrine disruption by postnatal diethylstilbestrol in neonatal mouse adrenal. *Chem Biol Interact* 182(2-3):253-8.

Louis GMB, Kim S, Chen Z, Sweeney AM, Barr D, Schrader SM. 2010. Polychlorinated biphenyls and semen quality–life study. *Fertil Steril* 94(4):S73-S74.

Lu Y, Azad N, Wang L, Iyer AKV, Castranova V, Jiang BH, Rojanasakul Y. 2010. Phosphatidylinositol-3-kinase/Akt regulates bleomycin-induced fibroblast proliferation and collagen production. *Am J Respir Cell Mol Biol* 42(4):432-441.

Luke NS, Sams R, DeVito MJ, Conolly RB, El-Masri HA. 2010. Development of a quantitative model incorporating key events in a hepatotoxic mode of action to predict tumor incidence. *Toxicol Sci* 115(1):253-266.

Magiatis P, Polychronopoulos P, Skaltsounis AL, Lozach O, Meijer L, Miller DB, O'Callaghan JP. 2010. Indirubins deplete striatal monoamines in the Intact and MPTP-treated mouse brain and block kainate-induced striatal astrogliosis. *Neurotoxicol Teratol* 32(2):212-219.

Makris SL, Euling SY, Gray LE, Jr, Benson R, Foster PM. 2010. Use of genomic data in risk assessment case study: I. Evaluation of the dibutyl phthalate male reproductive development toxicity data set. *Toxicol Appl Pharmacol*. Sept6 Epub ahead of print.

Marchetti F, Polyzos A, William A, Bishop J, Yauk C. 2010. Mainstream and sidestream tobacco smoke induce mutations in male germ cells but not micronuclei in erythrocytes in the mouse. *Environ Mol Mutagen* 51(7):705.

Marty MS., Allen B, Chapin RE, Cooper R, Daston GP, Flaws JA, Foster PM, Makris SL, Mylchreest E, Sandler D, Tyl RW. 2009. Inter-laboratory control data for reproductive endpoints required in the OPPTS 870.3800/OECD 416 reproduction and fertility test. *Birth Defects Res B Dev Reprod Toxicol* 86(6):470-489.

Mathews, JM, Watson, SL, Snyder, RW, Burgess, JP, and Morgan, DL. 2010. Reaction of the butter flavorant 2,3-butanedione with N-a-acetylarginine: A model for epitope formation with pulmonary proteins in the etiology of obliterative bronchiolitis. *J. Agric. Food Chem*. 58:12761-12768.

Mayo L, Dionne-Odom J, Talbot EA, Adamski C, Bean C, Daly ER, Gao F, Gougelet R, Montero J, Morse D, Smith J, Berry R, McGarry F, Wimsatt M, Stamm L, Madoff L, Gauthier C, Nalipinski M, Hoffmaster AR, Shadomy SV, Pesik NT, Smith TL, Rose LJ, Martinez K, Burrer SL, Stauffer K, Ctr Dis Control P. 2010. Gastrointestinal anthrax after an animal-hide drumming event - New Hampshire and Massachusetts, 2009. (Reprinted from MMWR, vol 59, pg 872-877, 2010). *JAMA* 304(10):1061-1064.

McCanlies EC, Yucesoy B, Mnatsakanova A, Slaven JE, Andrew M, Frye BL, Schuler CR, Kreiss K, Weston A. 2010. Association between IL-1A single nucleotide polymorphisms and chronic beryllium disease and beryllium sensitization. *J Occup Environ Med* 52(7):680-684.

McDaniel LP, Mittelstaedt RA, Dobrovolsky VN, Doerge DR, Ding W, Heflich RH. 2010. Genotoxicity of furan in Big Blue® Rats. *Environ Mol Mutagen* 51(7):728.

McKinney W, Chen B, Frazer D. 2009. Computer controlled multi-walled carbon nanotube inhalation exposure system. *Inhal Toxicol* 21(12):1053-1061.

Mei N, McDaniel LP, Dobrovolsky VN, Guo X, Shaddock JG, Mittelstaedt RA, Azuma M, Shelton SD, McGarrity LJ, Doerge DR, Heflich RH. 2010. The genotoxicity of acrylamide and glycidamide in Big Blue® rats. *Toxicol Sci* 115(2):412-421.

Mei N, Hu J, Xia Q, Fu PP, Moore MM, Chen T. 2010 Cytotoxicity and mutagenicity of retinol with ultraviolet A irradiation in mouse lymphoma cells. *Toxicol* In Vitro 24(2):439-444.

Methner M, Hodson L, Dames A, Geraci C. 2010. Nanoparticle emission assessment technique (NEAT) for the identification and measurement of potential inhalation exposure to engineered nanomaterials – Part B: results from 12 field studies. *J Occup Environ Hyg* 7(3):163-176.

Methner M, Hodson L, Geraci C. 2010. Nanoparticle emission assessment technique (NEAT) for the identification and measurement of potential inhalation exposure to engineered nanomaterials – Part A. *J Occup Environ Hyg* 7(3):127-132.

Minor RAC, Limmon GV, Miller-DeGraff L, Dixon D, Andrews DMK, Kaufman RJ, Imani F. 2010. Double-stranded RNA-activated protein kinase regulates early innate immune responses during respiratory syncytial virus infection. *J Interferon Cytokine Res* 30(4):263-272.

Misra N, Singh H, Hnizdo V. 2010. Nearest neighbor estimates of entropy for multivariate circular distributions. *Entropy* 12(5):1125-1144.

Mittelstaedt RA, Shaddock JG, Heflich RH. 2010. Comparison of responses in the *in vitro* flow cytometric micronucleus assay using CHO and TK6 cells. *Environ Mol Mutagen* 51(7):734.

Moon C, Park HJ, Choi YH, Park EM, Castranova V, Kang JL. 2010. Pulmonary inflammation after intraperitoneal administration of ultrafine titanium dioxide (TiO2) at rest or in lungs primed with lipopolysaccharide. *J Toxicol Environ Health A* 73(5-6):396-409.

Moore AB, Yu L, Swartz CD, Zheng X, Wang L, Castro L, Kissling GE, Walmer DK, Robboy SJ, Dixon D. 2010. Human uterine leiomyoma-derived fibroblasts stimulate uterine leiomyoma cell proliferation and collagen type I production, and activate RTKs and TGF beta receptor signaling in coculture. *Cell Commun Signal* 8:10.

Morrison TE, Montgomery SA, Oko L, Gunn B, Elmore SA, Heise MT. 2010. A mouse model of Chikungunya virus-induced musculoskeletal inflammatory disease: evidence of arthritis, tenosynovitis, and myositis. *Am J Pathol* 178(1):32-40.

Msiska Z, Pacurari M, Mishra A, Leonard SS, Castranova V, Vallyathan V. 2010. DNA double-strand breaks by asbestos, silica, and titanium dioxide: possible biomarker of carcinogenic potential? *Am J Respir Cell Mol Biol* 43(2):210-219.

Mutlu E, Collins LB, Stout MD, Upton PB, Daye LR, Winsett D, Hatch G, Evansky P, Swenberg JA. 2010. Development and application of an LC-MS/MS method for the detection of the vinyl chloride-induced DNA adduct N(2),3-Ethenoguanine in tissues of adult and weanling rats following exposure to [(13)C(2)]-VC. *Chem Res Toxicol* 23(9):1485-1491.

Nayak AP, Blachere FM, Hettick JM, Lukomski S, Schmechel D, Beezhold DH. 2010. Characterization of recombinant terrelysin, a hemolysin of Aspergillus terreus. *Mycopathologia* 171(1):23-34.

Neese SL, Wang VC, Doerge DR, Woodling KA, Andrade JE, Helferich WG, Korol DL, Schantz SL. 2010. Impact of dietary genistein and aging on executive function in rats. *Neurotoxicol Teratol* 32(2):200-211.

Pacurari M, Castranova V, Vallyathan V. 2010. Single- and multi-wall carbon nanotubes versus asbestos: are the carbon nanotubes a new health risk to humans? *J Toxicol Environ Health A* 73(5):378-95.

Page EH, Dowell CH, Charles A, Mueller CA, Biagini RE, Heederik D. 2010. Exposure to flour dust and sensitization among bakery employees. *Amer J Indust Med* 53:1225-1232.

Painter JT, Clayton NP, Herbert RA. 2010. Useful immunohistochemical markers of tumor differentiation. *Toxicol Pathol* 38(1):131-141.

Parham F, Austin C, Southall N, Huang R, Tice R, Portier C. 2009. Dose-response modeling of high-throughput screening data. *J Biomol Screen* 14(10):1216-27.

Parks CG, Biagini RE, Gilkeson GS, Dooley MA. 2010. Total serum IgE levels in systemic lupus erythematosus and associations with childhood onset allergies. *Lupus* 19:1614-1622.

Peng YY, Zhang QA, Snyder GL, Zhu HW, Yao W, Tomesch J, Papke RL, O'Callaghan JP, Welsh WJ, Wennogle LP. 2010. Discovery of novel alpha 7 nicotinic receptor antagonists. *Bioorg Med Chem Lett* 20(16):4825-4830.

Pereira SA, Tryndyak VP, Pogribny IP, Beland FA. 2010. Epigenetic markers of hepatotoxicity: a Nevirapine story. *Environ Mol Mutagen* 51(7):699-699.

Perez-De La Cruz V, Elinos-Calderon D, Carrillo-Mora P, Silva-Adaya D, Konigsberg M, Moran J, Ali SF, Chanez-Cardenas ME, Perez-De La Cruz G, Santamaria A. 2010. Time-course correlation of early toxic events in three models of striatal damage: Modulation by proteases inhibition. *Neurochem Int* 56(6-7):834-842.

Piper BJ, Ali SF, Daniels LG, Meyer JS. 2010. Repeated intermittent methylenedioxymethamphetamine exposure protects against the behavioral and neurotoxic, but not hyperthermic, effects of an MDMA binge in adult rats. *Synapse* 64(6):421-431.

Pogribny IP, Starlard-Davenport A, Tryndyak VP, Han T, Ross SA, Rusyn I, Beland FA. 2010. Difference in expression of hepatic microRNAs miR-29c, miR-34a, miR-155, and miR-200b is associated with strain-specific susceptibility to dietary nonalcoholic steatohepatitis in mice. *Lab Invest* 90(10):1437-1446.

Porter DW, Hubbs AF, Mercer RR, Wu N, Wolfarth MG, Sriram K, Leonard S, Battelli L, Schwegler-Berry D, Friend S, Andrew M, Chen BT, Tsuruoka S, Endo M, Castranova V. 2010. Mouse pulmonary dose- and time course-responses induced by exposure to multi-walled carbon nanotubes. *Toxicology* 269(2-3):136-147.

Prabhu BM, Ali SF, Murdock RC, Hussain SM, Srivatsan M. 2010. Copper nanoparticles exert size and concentration dependent toxicity on somatosensory neurons of rat. *Nanotoxicology* 4(2):150-160.

Rafii F, Park M, Gamboa da Costa G, Camacho L. 2009. Comparison of the metabolic activities of four wild-type Clostridium perfringens strains with their gatifloxacin-selected resistant mutants. *Arch Microbiol* 191(12):895-902.

Rao D, Rylander H, Drees R, Schwarz T, Steinberg H. 2010. Granular cell tumor in a lumbar spinal nerve of a dog. *J Vet Diagn Invest* 22(4):638-642.

Ramot Y, Nyska A, Lieuallen W, Maly A, Flake G, Kissling GE, Brix A, Malarkey DE, Hooth MJ. 2010. Inflammatory and chloracne-like skin lesions in B6C3F1 mice exposed to 3,3',4,4'-tetrachloroazobenzene for 2 years. *Toxicol* 265(1-2):1-9.

Ramot Y, Steiner M, Morad V, Leibovitch S, Amouyal N, Cesta MF, Nyska A. 2010. Pulmonary thrombosis in the mouse following intravenous administration of quantum dot-labeled mesenchymal cells. *Nanotoxicol* 4(1):98-105.

Rappaport SM, Kim S, Lan Q, Li G, Vermeulen R, Waidyanatha S, Zhang L, Yin S, Smith MT, Rothman N. 2010. Human benzene metabolism following occupational and environmental exposures. *Chem Biol Interact* 184(1-2):189-195.

Recio L, Hobbs C, Caspary W, Witt KL. 2010. Dose-response assessment of four genotoxic chemicals in a combined mouse and rat micronucleus (MN) and Comet assay protocol. *J Toxicol Sci* 35(2):149-162.

Reutman SR, Rohs AM, Clark JC, Johnson BC, Sammons DL, Toennis CA, Robertson SA, MacKenzie BA, Lockey JE. 2009. A pilot respiratory health assessment of nail technicians: symptoms, lung function, and airway inflammation. *Am J Ind Med* 52(11):868-75.

Rodriguez J, Jiang R, Johnson WC, MacKenzie BA, Smith LJ, Barr RG. 2010. The association of pipe and cigar use with cotinine levels, lung function, and airflow obstruction: a cross-sectional study. *Ann Intern Med* 152(4):201-210.

Ruminski AM, King BH, Salonen J, Snyder JL, Sailor MJ. 2010. Porous silicon-based optical microsensors for volatile organic analytes: Effect of surface chemistry on stability and specificity. *Adv Funct Mater* 20(17):2874-2883.

Ruwona TB, Johnson VJ, Schmechel D, Simoyi RH, Beezhold D, Siegel PD. 2010. Monoclonal antibodies against toluene diisocyanate haptenated proteins from vapor-exposed mice. Hybridoma (Larchmt) 29(3):221-229.

Ryman-Rasmussen JP, Cesta MF, Brody AR, Shipley-Phillips JK, Everitt JI, Tewksbury EW, Moss OR, Wong BA, Dodd DE, Andersen ME, Bonner JC. 2009. Inhaled carbon nanotubes reach the subpleural tissue in mice. *Nat Nanotechnol* 4(11):747-751.

Sadrieh, N, Wokovich, AM, Gopee, NV, Zheng, J, Haines, D, Parmiter, D, Siitonen, PH, Cozart, CR, Patri, AK, McNeil, SE, Howard, PC, Doub, WH and Buhse, LF (2010). Lack of significant dermal penetration of titanium dioxide from sunscreen formulations containing nano- and submicron-size TiO2 particles. *Toxicol Sci* 115(1):156-166.

Saito R, Cranmer BK, Tessari JD, Larsson L, Mehaffy JM, Keefe TJ, Reynolds SJ. 2009. Recombinant factor C (rFC) assay and gas chromatography/mass spectrometry (GC/MS) analysis of endotoxin variability in four agricultural dusts. *Ann Occup Hyg* 53(7):713-722.

Sarfaraz S, Tryndyak VP, Pognbny IP, Beland FA. 2010. Role of Genetic and Epigenetic Changes in Acrylamide-Induced Lung Carcinogenesis in Mice. *Environ Mol Mutagen* 51(7):712-712.

Sargent LM, Shvedova AA, Hubbs AF, Salisbury JL, Benkovic SA, Kashon ML, Lowry DT, Murray AR, Kisin ER, Friend S, McKinstry KT, Battelli L, Reynolds SH. 2009. Induction of aneuploidy by single-walled carbon nanotubes. *Environ Mol Mutagen* 50(8):708-717.

Schecter A, Colacino J, Patel K, Kannan K, Yun SH, Haffner D, Harris TR, Birnbaum L. 2010. Polybrominated diphenyl ether levels in foodstuffs collected from three locations from the United States. *Toxicol Appl Pharmacol* 243(2):217-224.

Schecter A, Haffner D, Colacino J, Patel K, Päpke O, Opel M, Birnbaum L. 2010 Polybrominated diphenyl ethers (PBDEs) and hexabromocyclodecane (HBCD) in composite U.S. food samples. *Environ Health Perspect* 118(3):357-362.

Schulte PA, Murashov V, Zumwalde R, Kuempel ED, Geraci CL. 2010. Occupational exposure limits for nanomaterials: state of the art. *J Nanoparticle Res* 12(6):1971-1987.

Shi L, Campbell G, Jones WD, Campagne F, Wen Z, Walker SJ, Su Z, Chu TM, Goodsaid FM, Pusztai L, Shaughnessy JD, Jr., Oberthuer A, Thomas RS, Paules RS, Fielden M, Barlogie B, Chen W, Du P, Fischer M, Furlanello C, Gallas BD, Ge X, Megherbi DB, Symmans WF, Wang MD, Zhang J, Bitter H, Brors B, Bushel PR, Bylesjo M, Chen M, Cheng J, Cheng J, Chou J, Davison TS, Delorenzi M, Deng Y, Devanarayan V, Dix DJ, Dopazo J, Dorff KC, Elloumi F, Fan J, Fan S, Fan X, Fang H, Gonzaludo N, Hess KR, Hong H, Huan J, Irizarry RA, Judson R, Juraeva D, Lababidi S, Lambert CG, Li L, Li Y, Li Z, Lin SM, Liu G, Lobenhofer EK, Luo J, Luo W, McCall MN, Nikolsky Y, Pennello GA, Perkins RG, Philip R, Popovici V, Price ND, Qian F, Scherer A, Shi T, Shi W, Sung J, Thierry-Mieg D, Thierry-Mieg J, Thodima V, Trygg J, Vishnuvajjala L, Wang SJ, Wu J, Wu Y, Xie Q, Yousef WA, Zhang L, Zhang X, Zhong S, Zhou Y, Zhu S, Arasappan D, Bao W, Lucas AB, Berthold F, Brennan RJ, Buness A, Catalano JG, Chang C, Chen R, Cheng Y, Cui J, Czika W, Demichelis F, Deng X, Dosymbekov D, Eils R, Feng Y, Fostel J, Fulmer-Smentek S, Fuscoe JC, Gatto L, Ge W, Goldstein DR, Guo L, Halbert DN, Han J, Harris SC, Hatzis C, Herman D, Huang J, Jensen RV, Jiang R, Johnson CD, Jurman G, Kahlert Y, Khuder SA, Kohl M, Li J, Li L, Li M, Li QZ, Li S, Li Z, Liu J, Liu Y, Liu Z, Meng L, Madera M, Martinez-Murillo F, Medina I, Meehan J, Miclaus K, Moffitt RA, Montaner D, Mukherjee P, Mulligan GJ, Neville P, Nikolskaya T, Ning B, Page GP, Parker J, Parry RM, Peng X, Peterson RL, Phan JH, Quanz B, Ren Y, Riccadonna S, Roter AH, Samuelson FW, Schumacher MM, Shambaugh JD, Shi Q, Shippy R, Si S, Smalter A, Sotiriou C, Soukup M, Staedtler F, Steiner G, Stokes TH, Sun Q, Tan PY, Tang R, Tezak Z, Thorn B, Tsyganova M, Turpaz Y, Vega SC, Visintainer R, von Frese,J, Wang C, Wang E, Wang J, Wang W, Westermann F, Willey JC, Woods M, Wu S, Xiao N, Xu J, Xu L, Yang L, Zeng X, Zhang J, Zhang L, Zhang M, Zhao C, Puri RK, Scherf U, Tong W, Wolfinger RD. 2010. The MicroArray Quality Control (MAQC)-II study of common practices for the development and validation of microarray-based predictive models. *Nat Biotechnol* 28(8):827-838.

Shi Q, Guo L, Patterson TA, Dial S, Li Q, Sadovova N, Zhang X, Hanig JP, Paule MG, Slikker W, Jr. Wang C. 2010. Gene expression profiling in the developing rat brain exposed to ketamine. *Neuroscience* 166(3):852-863.

Shim M, Foley J, Anna C, Mishina Y, Eling T. 2010. Embryonic expression of cyclooxygenase-2 causes malformations in axial skeleton. *J Biol Chem* 285(21):16206-16217.

Shpyleva SI, Tryndyak VP, Kovalchuk O, Starlard-Davenport A, Chekhun VF, Beland FA, Pogribny IP. 2010. Role of ferritin alterations in human breast cancer cells. *Breast Cancer Res Treat* 126(1)63-71

Shvedova AA, Kagan VE. 2010. The role of nanotoxicology in realizing the 'helping without harm' paradigm of nanomedicine: lessons from studies of pulmonary effects of single-walled carbon nanotubes. *J Intern Med* 267(1):106-118.

Shvedova AA, Kagan VE. Fadeel B. 2010. Close encounters of the small kind: adverse effects of man-made materials interfacing with the nano-cosmos of biological systems. *Annu Rev Pharmacol Toxicol* 50:63-88.

Siegel PD, Fowler JF, Storrs FJ, Sasseville D, Pratt M, Bledsoe TA, Law BF, Beezhold D, Zug K, Fowler LM. 2010. Allergen content of patient problem and nonproblem gloves: relationship to allergen-specific patch-test findings. *Dermatitis* 21(2):77-83.

Siegel PD, Law BF, Fowler JF Jr., Fowler LM. 2010. Disproportionated rosin dehydroabietic acid in neoprene surgical gloves. *Dermatitis* 21(3):157-159.

Singh BP, Nyska A, Kissling GE, Lieuallen W, Johansson SL, Malarkey DE, Hooth MJ. 2010. Urethral carcinoma and hyperplasia in male and female B6C3F1 mice treated with 3,3 ',4,4 '-tetrachloroazobenzene (TCAB). *Toxicol Pathol* 38(3):372-381.

Slikker W, Liu F, Zhang X, Xou X, Patterson T, Paule M, Wang C. 2010. Genomic response to perinatal anesthetic-induced neuronal cell death. *Birth Defects Res A Clin Mol Teratol* 88(5):379-379.

Smith J, Sammons D, Robertson S, Biagini R, Snawder J. 2010. Measurement of multiple drugs in urine, water, and on surfaces using fluorescence covalent microbead immunosorbent assay. *Toxicol Mech Methods* 20:587-593.

Smoak KA, Aloor JJ, Madenspacher J, Merrick BA, Collins JB, Zhu X, Cavigiolio G, Oda MN, Parks JS, Fessler MB. 2010. Myeloid differentiation primary response protein 88 couples reverse cholesterol transport to inflammation. *Cell Metab* 11(6):493-502.

Sriram K, Lin GX, Jefferson AM, Roberts JR, Chapman RS, Chen BT, Soukup JM, Ghio AJ, Antonini JM. 2010. Dopaminergic neurotoxicity following pulmonary exposure to manganese-containing welding fumes. *Arch Toxicol* 84(7):521-540.

Sriram K, Lin GX, Jefferson AM, Roberts JR, Wirth O, Hayashi Y, Krajnak KM, Soukup JM, Ghio AJ, Reynolds SH, Castranova V, Munson AE, Antonini JM. 2010. Mitochondrial dysfunction and loss of Parkinson's disease-linked proteins contribute to neurotoxicity of manganese-containing welding fumes. *FASEB J* 24(12):4989-5002.

Starlard-Davenport A, Tryndyak V, Kosyk O, Ross SR, Rusyn I, Beland FA, Pogribny IP. 2010. Dietary methyl deficiency, microRNA expression and susceptibility to liver carcinogenesis. *World Rev Nutr Diet* 101:123-130.

Starlard-Davenport A, Tryndyak VP, James SR, Karpf AR, Latendresse JR, Beland FA, Pogribny IP. 2010. Mechanisms of epigenetic silencing of the Rassf1a gene during estrogen-induced breast carcinogenesis in ACI rats. *Carcinogenesis* 31(3):376-381.

Stefaniak AB, Harvey CJ, Bukowski VC, Leonard SS. 2010. Comparison of free radical generation by pre- and post-sintered cemented carbide particles. *J Occup Environ Hyg* 7(1):23-24.

Swartz CD, Lentz CA, Green AS, Prajapati MH, Recio L, Witt KL. 2010. Mutagenicity of three herbal products, pulegone, senna, and milk thistle extract, in the Ames Salmonella mutagenicity assay. *Environ Mol Mutagen* 51(7):718-718.

Templeton SP, Buskirk AD, Green BJ, Beezhold DH, Schmechel D. 2010. Murine models of airway fungal exposure and allergic sensitization. *Med Mycol* 48(2):217-228.

Teng CT. 2010. Lactoferrin: the path from protein to gene. *Biometals* 23(3):359-364.

Thigpen J, Kissling G, Collins B, Setchell K, Adsit F, Caviness G, Locklear J, Whiteside T, Grant M, Forsythe D. 2010. The impact of rodent diets and bedding in studies evaluating the estrogenic activity of endocrine disruptor compounds. *J Am Assoc Lab Anim Sci* 49(5):748.

Thomas AC, Nouls JC, Driehuys B, Voltz JW, Fubara B, Foley J, Bradbury JA, Zeldin DC. 2010. Ventilation defects observed with hyperpolarized 3He magnetic resonance imaging in a mouse model of acute lung injury. *Am J Respir Cell Mol Biol* 2010 Jul 1 Epub ahead of print.

Tokar EJ, Benbrahim-Tallaa L, Ward JM, Lunn R, Sams RL 2nd, Waalkes MP. 2010. Cancer in experimental animals exposed to arsenic and arsenic compounds. *Crit Rev Toxicol* 40(10):912-927.

Tokar EJ, Diwan BA and Waalkes MP. 2010. Arsenic exposure transforms human epithelial stem/progenitor cells into a cancer stem-like phenotype. *Environ Health Perspect* 118(1):108-115.

Tokar EJ, Diwan BA, Waalkes MP. 2010. Arsenic exposure *in utero* and nonepidermal proliferative response in adulthood in Tg.AC mice. *Int J Toxicol* 29(3):291-296.

Tokar EJ, Diwan BA, Waalkes MP. 2010. Early life inorganic lead exposure induces testicular teratoma and renal and urinary bladder preneoplasia in adult metallothionein-knockout mice but not in wild type mice. *Toxicology* 276(1):5-10.

Tokar EJ, Qu W, Liu J, Liu W, Webber MM, Phang JM, Waalkes MP. 2010. Arsenic-specific stem cell selection during malignant transformation. *J Natl Cancer Inst* 102(9):638-649.

Trembath D, Rao D, Morrison J, Malarkey D. 2010. Comparative pathology of medulloblastoma in F-344 rats and humans. *J Neuropath Exp Neurol* 69(5):30.

Tryndyak VP, Beland FA, Pogribny IP. 2010. E-cadherin transcriptional down-regulation by epigenetic and microRNA-200 family alterations is related to mesenchymal and drug-resistant phenotypes in human breast cancer cells. *Int J Cancer* 126(11):2575-2583.

Tubbs JT, Blankenship-Paris T, Travlos G, King-Herbert AP, Kissling G, Clark J, Goulding D. 2010. Buprenorphine, meloxicam, and flunixin meglumine postoperative analgesia in mice. *J Am Assoc Lab Anim Sci* 49(5):692-692.

Turpin EA, Antao-Menezes A, Cesta MF, Mangum JB, Wallace DG, Bermudez E, Bonner JC. 2010. Respiratory syncytial virus infection reduces lung inflammation and fibrosis in mice exposed to vanadium pentoxide. *Respir Res* 11:20.

Tvermoes BE, Boyd WA, Freedman JH. 2010. Molecular characterization of numr-1 and numr-2: genes that increase both resistance to metal-induced stress and lifespan in Caenorhabditis elegans. *J Cell Sci* 123(Pt 12):2124-2134.

Tyl RW, Seely JC, Marr MC, Myers CB, Youn VY, Browning DB, Bishop JB. 2010. Gonadal responses to vinclozolin administered orally to Han Wistar Rats. *Birth Defects Res A Clin Mol Teratol* 88(5):358-358.

Wan YW, Qian Y, Rathnagiriswaran S, Castranova V, Guo NL. 2010. A breast cancer prognostic signature predicts clinical outcomes in multiple tumor types. *Oncol Rep* 24(2):489-494.

Wan YW, Sabbagh E, Raese R, Qian Y, Luo DJ, Denvir J, Vallyathan V, Castranova V, Guo NL. 2010. Hybrid models identified a 12-gene signature for lung cancer prognosis and chemoresponse prediction. *PLoS One* 5(8):e12222

Wang C, Zhang XA, Liu F, Paule MG, Slikker W. 2010. Anesthetic-induced oxidative stress and potential protection. *Sci World J* 10:1473-1482.

Wang J, Rahman MF, Duhart HM, Newport GD, Patterson TA, Murdock RC, Hussain SM, Schlager JJ, Ali SF. 2009. Expression changes of dopaminergic system-related genes in PC12 cells induced by manganese, silver, or copper nanoparticles. *Neurotoxicology* 30(6):926-933.

Wang L, Mercer RR, Rojanasakul Y, Qiu A, Lu Y, Scabilloni JF, Wu N, Castranova V. 2010. Direct fibrogenic effects of dispersed single-walled carbon nanotubes on human lung fibroblasts. *J Toxicol Environ Health A* 73(5):410-422.

Wang RS, McDaniel LP, Manjanatha MG, Shelton SD, Doerge DR, Mei N. 2010. Mutagenicity of acrylamide and glycidamide in the testes of big blue mice. *Toxicol Sci* 117(1):72-80.

Ward EM, Schulte PA, Straif K, Hopf NB, Caldwell JC, Carreón T, DeMarini DM, Fowler BA, Goldstein BD, Hemminki K, Hines CJ, Pursiainen KH, Kuempel E, Lewtas J, Lunn RM, Lynge E, McElvenny DM, Muhle H, Nakajima T, Robertson LW, Rothman N, Ruder AM, Schubauer-Berigan MK, Siemiatycki J, Silverman D, Smith MT, Sorahan T, Steenland K, Stevens RG, Vineis P, Zahm SH, Zeise L, Cogliano VJ. 2010. Research recommendations for selected IARC-classified agents. *Environ Health Perspect* Epub 2010 Jun 18.

Waters MA, Grajewski B, Pinkerton LE, Hein MJ, Zivkovich Z. 2009. Development of historical exposure estimates of cosmic radiation and circadian rhythm disruption for cohort studies of Pan Am flight attendants. *Am J Ind Med* 52(10): 751-761.

Whaley MJ, Rose C, Martinez J, Laher G, Sammons DL, Smith JP, Snawder JE, Borrow R, Biagini RE, Plikaytis B, Carlone GM, Romero-Steiner S. 2010. Interlaboratory comparison of three multiplexed bead-based immunoassays for measuring serum antibodies to pneumococcal polysaccharides. *Clin Vaccine Immunol* 17(5):862-869.

Witt KL, Malarkey DE, Hobbs CA, Davis JP, Kissling GE, Caspary W, Travlos G, Recio L. 2010. No increases in biomarkers of genetic damage or pathological changes in heart and brain tissues in male rats administered methylphenidate hydrochloride (Ritalin) for 28 days. *Environ Mol Mutagen* 51(1):80-88.

Wu N, Wang J, Tafen DN, Wang H, Zheng JG, Lewis JP, Liu X, Leonard SS, Manivannan A. 2010. Shape-enhanced photocatalytic activity of single-crystalline anatase TiO2 (101) Nanobelts. *J Am Chem Soc* 132(19):6679-6685.

Yoshizawa K, Brix AE, Sells DM, Jokinen MP, Wyde M, Orzech DP, Kissling GE, Walker NJ, Nyska A. 2009. Reproductive lesions in female Harlan Sprague-Dawley rats following two-year oral treatment with dioxin and dioxin-like compounds. *Toxicol Pathol* 37(7):921-937.

Yu L, Moore AB, Dixon D. 2010. Receptor tyrosine kinases and their hormonal regulation in uterine leiomyoma. *Semin Reprod Med* 28(3):250-259.

Yuan BZ, Chapman J, Reynolds SH. 2009. Proteasome inhibitors induce apoptosis in human lung cancer cells through a positive feedback mechanism and the subsequent Mcl-1 protein cleavage. *Oncogene* 28(43):3775-3786.

Yucesoy B, Johnson VJ, Fluharty K, Kashon ML, Slaven JE, Wilson NW, Weissman DN, Biagini RE, Germolec DR, Luster MI. 2009. Influence of cytokine gene variations on immunization to childhood vaccines. *Vaccine* 27(50):6991-6997.

Zegre Cannon C, Kissling G, J Hoenerhoff M, King-Herbert A, Blankenship-Paris T. 2010. Evaluation of dosages and routes of administration of tramadol analgesia in rats using hot-plate and tail-flick tests. *Lab Anim* 39:342-351.

Zeidler-Erdely PC, Kashon ML, Li SQ, Antonini JM. 2010. Response of the mouse lung transcriptome to welding fume: effects of stainless and mild steel fumes on lung gene expression in A/J and C57BL/6J mice. *Respir Res* 11:70.

Zhang D, Hu X, Qian L, O'Callaghan JP, Hong JS. 2010. Astrogliosis in CNS pathologies: Is there a role for microglia? *Mol Neurobiol* 41(2-3):232-241.

Zhang XD, Zhao JS, Bowman L, Shi XG, Castranova V, Ding M. 2010. Tungsten carbide-cobalt particles activate Nrf2 and its downstream target genes in JB6 cells possibly by ROS generation. *J Environ Pathol Toxicol Oncol* 29(1):31-40.

Zhang YB, Ali SF, Dervishi E, Xu Y, Li ZR, Casciano D, Biris AS. 2010. Cytotoxicity effects of graphene and single-wall carbon nanotubes in neural phaeochromocytoma-derived PC12 Cells. *ACS Nano* 4(6):3181-3186.

Zhu H, O'Brien JJ, O'Callaghan JP, Miller DB, Zhang Q, Rana M, Tsui T, Peng Y, Tomesch J, Hendrick JP, Wennogle LP, Snyder GL. 2010. Nerve agent exposure elicits site-specific changes in protein phosphorylation in mouse brain. *Brain Res* 1342(C):11-23

National Toxicology Program
U.S. Department of Health and Human Services

National Toxicology Program
PO Box 12233
111 TW Alexander Drive
Research Triangle Park, NC 27709
www.ntp.niehs.nih.gov

NIH Publication No. 11-5972